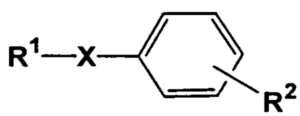
[File Name] SPECIFICATION

[Title of the Invention] Dicarba-*closo*-Dodecaborane Derivatives

[Claims]

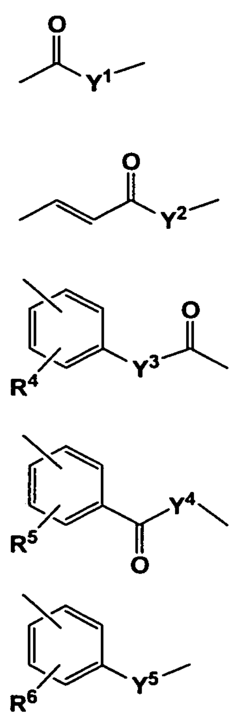
[Claim 1] A medicament comprising as an active ingredient a compound or a physiologically acceptable salt thereof represented by the following general formula (I) :

[Formula 1]



wherein R^1 represents a dicarba-*closo*-dodecaboran-yl group which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a mono- or di-lower alkylcarbamoyl-substituted alkyl group, a lower alkanoyl group, an aryl group which may be substituted, and a lower aralkyl group which may be substituted; R^2 represents carboxyl group, a lower alkoxy carbonyl group, or hydroxyl group ; X represents a single bond or a linking group selected from the group consisting of the groups represented by the following formulas:

[Formula 2]



wherein, Y^1, Y^2, Y^3, Y^4, and Y^5 independently represent oxygen atom or -N(R^3)- wherein R^3 represents hydrogen atom or a lower alkyl group; and R^4, R^5, and R^6 independently represents hydrogen atom or one or more substituents on the phenyl group.

[Claim 2] The medicament according to claim 1 comprising as an active ingredient the compound or a physiologically acceptable salt thereof represented by the formula (I) wherein R^1 is a dicarba-*closo*-dodecaboran-yl group which may have a lower alkyl group, R^2 is carboxyl group or a lower alkoxycarbonyl group, and X is the above-defined linking group.

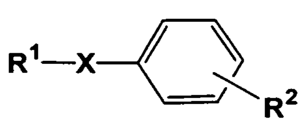
[Claim 3] The medicament according to claim 1 comprising as an active ingredient the compound or a physiologically acceptable salt thereof represented by the formula (I) wherein R^1 is a dicarba-*closo*-dodecaboran-yl group which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a lower alkanoyl group, a phenyl group, hydroxyphenyl group, and a lower alkoxyphenyl group, R^2 is hydroxyl group, and X is a single bond.

[Claim 4] The medicament according to any of claim 1 to 3, used as an agent for therapeutic treatment of leukemia.

[Claim 5] A medicament comprising a compound having a dicarba-*closo*-dodeca-boran-yl group as a hydrophobic pharmacophore.

[Claim 6] A compound or a salt thereof represented by the following general formula (I) :

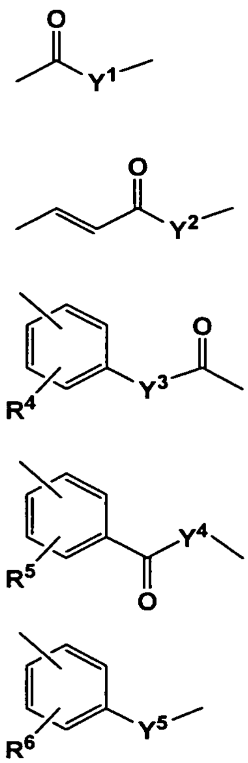
[Formula 3]



wherein R^1 represents a dicarba-*closo*-dodecaboran-yl group which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a mono or di-lower alkylcarbamoyl-substituted alkyl group, a lower alkanoyl group, an aryl group which may be substituted, and a lower aralkyl

group which may be substituted; R^2 represents carboxyl group, a lower alkoxy carbonyl group, or hydroxyl group; X represents a single bond or a linking group selected from the group consisting of the groups represented by the following formulas ;

[Formula 4]



wherein, Y^1, Y^2, Y^3, Y^4, and Y^5 independently represents oxygen atom or -N(R^3)- wherein R^3 represents hydrogen atom or a lower alkyl group; and R^4, R^5, and R^6 independently represents hydrogen atom or one or more substituents on the phenyl group,

provided that when X is a single bond,

the compound wherein R^1 is unsubstituted dicarba-*closo*-dodecaboran-yl group and R^2 is hydroxyl group, and

the compound wherein R^1 is dicarba-*closo*-dodecaboran-yl group substituted with p-hydroxyphenyl group and R^2 is hydroxyl group

are excluded.

[Claim 7] The compound or a salt thereof according to claim 5, wherein R^1 is a dicarba-*closo*-dodecaboran-yl group which may have a lower alkyl, R^2 is carboxyl group or a lower alkoxycarbonyl group, and X is the above-defined linking group.

[Claim 8] The compound or a salt thereof according to claim 5, wherein R^1 is a dicarba-*closo*-dodecaboran-yl group which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a lower alkanoyl group, a phenyl group, hydroxyphenyl group, and a lower alkoxyphenyl group, R^2 is hydroxyl group, and X is a single bond.

[Detailed Explanation of the Invention]

[0001]

The present invention relates to a novel dicarba-*closo*-dodecaborane derivative. The present invention also relates to a medicament comprising said dicarba-*closo*-dodecaborane derivative as an active ingredient.

[0002]

[Prior Art]

Dicarba-*closo*-dodecaborane (hereinafter abbreviated as "carborane" in the specification) is an icosahedral cluster containing two carbon atoms and ten boron atoms in which both atoms are hexacordinated. In caboranes, depending on the position of the carbon atoms in the cluster, 3 kinds of isomers exist, i.e., 1,2-dicarba-*closo*-dodecarobane (*ortho*-carborane), 1,7- dicarba-*closo*-dodecaborane (*meta*-carborane), and 1,12-dicarba-*closo*-dodeca borane (*para*-carborane). These structures are unique among boron compounds, namely they are characterized to have very high thermal stability and hydrophobicity comparable to hydrocarbons.

[0003]

A major utility of compounds composed of a carborane so far has been an application to ^{10}Boron-Neutron Capture Therapy (BNCT). ^{10}Boron-Neutron Capture Therapy has been developed as a therapy mainly to glioma and melanoma. When ^{10}B atom is irradiated with thermal neutron (slow neutron), an α ray with 2.4 MeV energy is emitted and the atom is decomposed to ^{7}Li and ^{4}He. The range of α ray is about 10 μm which corresponds to a diameter of cells. Therefore, effects are expected that only cells in which ^{10}B atoms are uptaken are destroyed and other cells are not damaged. For the development of BNCT, it is important how to have cancer cells selectively uptake ^{10}B atoms in a concentration capable of destroying cells with neutron radiation. For that purpose, *ortho*-carborane skeleton has been utilized

which has low toxicity and a high ^{10}B atom content, and is easy to be synthesized. Moreover, nucleic acid precursors, amino acids, and porphyrins which contain *ortho*-carboranes have been synthesized and subjected to evaluation.

[0004]

[Objects to be Achieved by the Invention]

Studies on carborane compounds have been focused solely on creation of compounds suitable for BNCT, and therefore, for a purpose of introducing carboranes into cells, designs have been made in which carborane skeletons are attached to compounds with biological roles. However, the conventional studies are far from drug designs which utilizes properties of the carboranes per se for molecular recognition in vivo. An object of the present invention is to provide novel bioactive substances which utilize a carborane as a hydrophobic pharmacophore for a partial structure of a medicament on the basis of understanding of physical and chemical properties of carboranes.

[0005]

Generally, hydrogen bonding and shape of molecule as well as hydrophobic interaction contribute to stabilization of a ligand-receptor complex. Accordingly, it is considered that introduction of a carborane as a hydrophobic moiety may increase the stability of a ligand-receptor complex and enhance a desirable biological activity. Carborane-containing nuclear receptor ligands provided by the present invention are promising compounds for application to BNCT from a viewpoint of targeting to cancer cells. As agents acting on nuclear receptors, they are expected to have pharmacodynamics different from that of conventional drugs while exhibiting superior activities.

[0006]

An object of the present invention is to provide a bioactive compound having a carborane skeleton as a pharmacophore. More specifically, the object is to provide a novel compound which has a superior bioactivity and is useful as a regulating agent on a nuclear receptor with reduced cytotoxicity. Another object of the present invention is to provide a medicament comprising said compound as an active ingredient which is useful as an agent for differentiation-inducing therapy for leukemia and an estrogenic agent.

[0007]

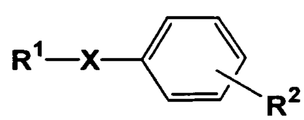
[Means to Solve the Problem]

As a result of zealous endeavor of the inventors of the present invention to solve the foregoing objects, the inventors found that a compounds having a dicarba-*closo*-dodecaborane structure represented by the following general formula (I) has superior activity as a ligand of a nuclear receptor such as the retinoic acid receptor and exhibits a superior therapeutic effect as a differentiation-inducing agent for the treatment of leukemia. The present invention was achieved on the basis of these findings.

[0008]

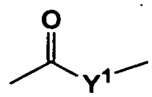
The present invention thus provides a medicament which comprises as an active ingredient a compound or a physiologically acceptable salt thereof represented by the following general formula (I) :

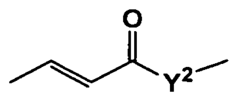
[Formula 5]

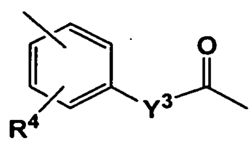


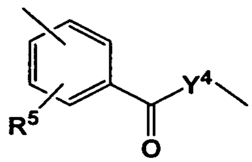
wherein R_1 represents a dicarba-*closo*-dodecaboran-yl group which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a mono or di-lower alkylcarbamoyl-substitute alkyl group, a lower alkanoyl group, an aryl group which may be substituted, and a lower aralkyl group which may be substituted; R^2 represents carboxyl group, a lower alkoxycarbonyl group, or hydroxyl group; X represents a single bond, or a linking group selected from the group consisting of groups represented by the following formulas:

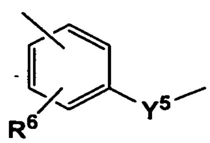
[Formula 6]











[wherein Y^1, Y^2, Y^3, Y^4, and Y^5 independently represent oxygen atom or -N(R^3)- (wherein R^3 represents hydrogen atom or a lower alkyl group); and R^4, R^5, and R^6 independently represent hydrogen atom or one or more substituents on the phenyl group].

[0009]

According to preferred embodiments of the aforementioned invention, provided are:

(1) a medicament comprising as an active ingredient the compound or a physiologically acceptable salt thereof represented by the aforementioned formula (I) wherein R^1 is a dicarba-*closo*-dodecaboran-yl group which may have a lower alkyl group, R^2 is carboxyl group or a lower alkoxycarbonyl group, and X is the aforementioned linking group; and

(2) a medicament comprising as an active ingredient the compound or a physiologically acceptable salt thereof represented by the aforementioned formula (I) wherein R^1 represents a dicarba-*closo*-dodecaboran-yl group which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a lower alkanoyl group, phenyl group, hydroxyphenyl group, and a lower alkoxyphenyl group, R^2 represents hydroxyl group, and X is a single bond.

[0010]

The compound represented by the aforementioned formula (I) or a physiologically acceptable salt thereof can act as a ligand of a nuclear receptor. Therefore, the medicament is useful as an agent as a retinoid or an estrogenic agent, and also useful for therapeutic and/or prophylactic treatment of cancer, rheumatism, arteriosclerosis, diabetes, rejection reaction in case of an organ transplantation, and graft versus host disease. Particularly, the aforementioned medicament comprising the compound defined by (1) or a physiologically acceptable salt thereof can be used, for example, for therapeutic treatment of leukemia as an agent having retinoid action. The aforementioned medicament comprising the compound defined by (2) or a physiologically acceptable salt thereof is useful as an estrogenic agent, for example, for the prophylactic and/or therapeutic treatment of menstrual disorders, osteoporosis, or cancer.

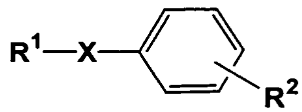
[0011]

From another aspect, the present invention provides a use of the compound represented by the above formula (I) or a salt thereof for the manufacture of the aforementioned medicament; a method for therapeutic treatment of leukemia which comprises the step of administering to a patient a therapeutically effective amount of the compound represented by the aforementioned formula (I) or a physiologically acceptable salt thereof, preferably the compounds defined by the aforementioned (1) or a physiologically acceptable salt thereof; and a method for therapeutic and/or prophylactic treatment of a solid cancer or a serious dermatosis which comprises the step of administering to a patient a therapeutically effective amount of the compound represented by the aforementioned formula (I) or a physiologically acceptable salt thereof, preferably the compounds defined by the aforementioned (1) or a physiologically acceptable salt thereof.

[0012]

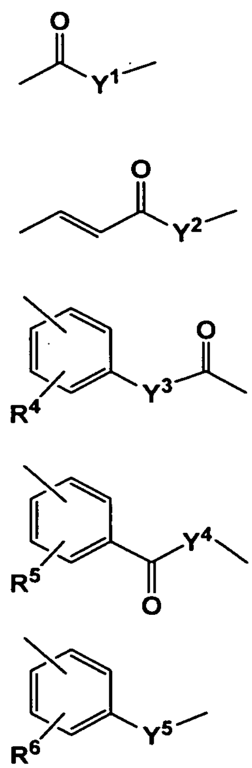
From further aspect, the present invention provides, as a novel substance, the compound or a salt thereof represented by the following formula (I):

[Formula 7]



wherein R^1 represents dicarba-*closo*-dodecaboran-yl group which may have a substituent selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a mono or di-lower alkyl carbamoyl-substituted alkyl group, a lower alkanoyl group, an aryl group which may be substituted, and a lower aralkyl group which may be substituted; R^2 represents carboxyl group, a lower alkoxycarbonyl group, or hydroxyl group; X represents a single bond or a linking group selected from the group consisting of the groups represented by the following formulas;

[Formula 8]



[wherein, Y^1, Y^2, Y^3, Y^4 and Y^5 independently represent oxygen atom or -N(R^3) - (wherein R^3 represents hydrogen atom or a lower alkyl group); and R^4, R^5, and R^6 independently represent hydrogen atom or one or more substituents on the phenyl group], provided, when X is a single bond, the compound wherein R^1 is a non-substituted dicarba-*closo*-dodecaboran-yl group and R^2 is a hydroxyl group, and

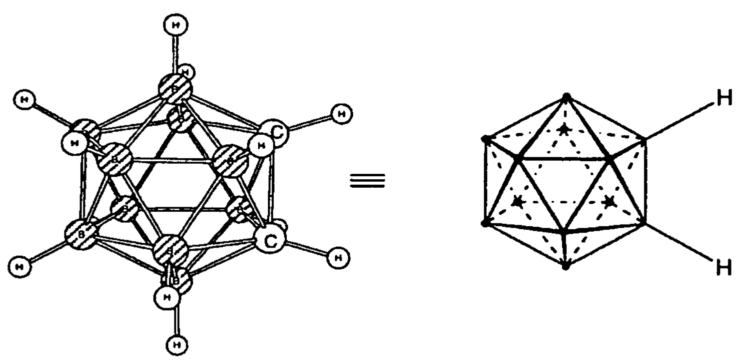
the compound wherein R^1 is a dicarba-*closo*-dodecaboran-yl group substituted with p-hydroxyphenyl group and R^2 is a hydroxyl group are excluded.

[0013]

[Mode for Carrying Out the Invention]

1,2-Dicarba-*closo*-dodecaborane (*ortho*-carborane) is a compound represented by the following formula. The compound has ten boron atoms expressed as "B" in the formula each having a hydrogen atom and two carbon atoms expressed as "C" in the formula each having a hydrogen atom.

[Formula 9]



[0014]

1,2-Dicarba-*closo*-dodecaboran-1-yl group corresponds to a residual group formed by eliminating a hydrogen atom on one carbon atom in the carborane ring of the formula. When the aforementioned group has a substituent, the substituent is on the 2-position carbon atom. As dicarba-*closo*-dodecaboranes, 1,7-dicarba-*closo*-dodecaboranes (*meta*-carborane) and 1,12-dicarba-*closo*-dodecaborane (*para*-carborane) are also known. These can form 1,7-dicarba-*closo*-dodecaboran-1-yl group and 1,12-dicarba-*closo*-dodecaboran-1-yl group similarly to the *ortho*-carborane, and may have a substituent on the 7-position carbon and 12-position carbon, respectively. The term "dicarba-*closo*-dodecaboran-yl group" used herein encompasses residues of the three isomers of dicarba-*closo*-dodecaboranes.

[0015]

The medicament of the present invention are characterized to have a dicarba-*closo*-dodecaboran-yl group as a hydrophobic pharmacophore. A biopolymer

molecule represented by a receptor, hereafter simply referred to as "receptor", has a characteristic structure as a partial structure which recognizes a drug, thereby forms stable bonds through spatial interaction with the drug and exhibits its bioaction. Plural functional groups or group composed thereof involved in the interaction are called "pharmacophore." A hydrophobic part of a drug stabilizes the bonds through hydrophobic interaction with the binding site of a receptor and has a significant role in recognition of a drug structure by a receptor.

[0016]

The term "hydrophobic pharmacophore" in the compound of the present invention means a partial structure of a pharmaceutical compound and a structure which, as a hydrophobic moiety, has contribution or is expected to have contribution to bond stabilization with a receptor. The compound of the present invention has a dicarba-*closo*-dodecaboran-yl group as a hydrophobic pharmacophore and can be used as a medicament. Particularly, said compound can act as an agonist or an antagonist to a nuclear receptor to which a nuclear receptor ligand such as retinoid, estrogen, androgen or thyroid binds. Some compounds having a dicarba-*closo*-dodecaboran-yl group have been studied for application to BNCT. However, use of a dicarba-*closo*-dodecaboran-yl group as a hydrophobic pharmacophore, for a purpose of achieving binding stability with a receptor and enhancing bioactivity based on the binding stability, has not been reported.

[0017]

In the specification, the lower alkyl or a lower alkyl moiety of a functional group that contains the lower alkyl moiety (e.g., the lower alkoxycarbonyl group, the lower alkenyl group, the lower hydroxyalkyl group, the lower alkanoyl group, the lower aralkyl group and the like) may be linear, branched, cyclic, or a combination thereof, and the number of carbon atom is from 1 to 6, preferably from 1 to 4. As the lower alkyl group, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, isobutyl group, tert-butyl group can be used. As the lower alkenyl group, those having 1 to 6 carbon atoms can be used. The number of double bonds contained in the lower alkenyl group is not limited, and the number may generally be one to three, preferably one.

[0018]

Substituents which can be present on a dicarba-*closo*-dodecaboran-yl group will be specifically explained. Examples of the lower alkoxy carbonyl group include methoxycarbonyl group, ethoxy carbonyl group and the like. The amino group may have one or two substituents, for example, a lower alkyl group and a lower alkanoyl group. Examples of the lower hydroxyalkyl group include hydroxymethyl group, 2-hydroxyethyl group, 1-hydroxyethyl group and the like. Examples of the lower alkanoyl group include acetyl group, propanoyl group and the like.

[0019]

The number of carbon atoms of the alkyl group substituted with mono or di lower alkyl-substituted carbamoyl group is from 1 to 12, preferably about from 8 to 10. Phenyl group is preferable as the aryl group, and benzyl group is preferred as the aralkyl group. A lower alkyl group, a halogen atom, hydroxyl group, a lower alkoxy group and the like may be used as a substituent on the ring of the aryl group or the aralkyl group. A mono or di-lower alkyl-substituted amino group, or a cyclic amino group (e.g., pyrrolidinyl group, piperidinyl group and the like) may be a substituent on the lower alkoxy group on the ring. The positions of substituents on the aryl ring are not limited, but *para* position is preferred.

[0020]

As the lower alkoxycarbonyl group represented by R^2, for example, ethoxy carbonyl group, methoxy carbonyl group and the like are preferred. R^2 may substitute in any position of the benzene ring, and preferably substitute in the *para* position. Y^1, Y^2, Y^3, Y^4 and Y^5 may preferred be a group represented by $-N(R^3)-$, and as the lower alkyl group represented by R^3, the alkyl group specifically explained above can be suitably used. R^3 is preferably hydrogen atom or methyl group. When R^4, R^5 and R^6 are substituents on the phenyl group, the kind, number, and position of the substituents are not particularly limited. Examples of the substituent on the phenyl group include, for example, a lower alkyl group, a lower alkoxy group, a lower alkoxycarbonyl group, a halogen atom, carboxyl group, amino group, an alkanoyl group, an aralkyl group, hydroxyl group, however, the substituents are not limited to these examples.

[0021]

R^4, R^5 and R^6 are preferably hydrogen atoms. When Y^5 is $-N(R^3)-$ (R^3

represents a lower alkyl group, preferably methyl group), R^6 is preferably a lower alkyl group, for example, methyl group. When R^1 binds to the phenyl group in X, the binding position is not limited. Preferably, R^1 binds to the phenyl group in the *meta* or *para* position relative to the nitrogen atom or the carbonyl group present in X. When X is a single bond, R^1 binds directly to the phenyl group substituted with R^2.

[0022]

More specifically, a preferred embodiment of the present invention includes (1) a compound of formula (I) wherein R^1 is dicarba-*closo*-dodecaboran-yl group which may have a lower alkyl group, R^2 is carboxyl group or a lower alkoxycarbonyl group, and X is the aforementioned linking group. In the aforementioned compound, each of Y^1, Y^2, Y^3, Y^4 and Y^5 is preferably a group represented by -N(R^3)-, and R^3 is preferably hydrogen atom. Each of R^4, R^5 and R^6 is preferably hydrogen atom. When Y^5 is -N(R^3)- (wherein R^3 is a lower alkyl group, preferably methyl group), R^6 is preferably a lower alkyl group, for example, methyl group.

[0023]

Another preferred compound includes (2) a compounds of formula (I) wherein R^1 is dicarba-*closo*-dodecaboran-yl group which may have one or more substituents selected from the group consisting of a lower alkyl group, a lower alkenyl group, carboxyl group, a lower alkoxycarbonyl group, amino group, a lower hydroxyalkyl group, a lower alkanoyl group, phenyl group, hydroxyphenyl group, and a lower alkoxyphenyl group, R^2 is a hydroxyl group, and X is a single bond.

[0024]

The compound represented by formula (I) may have one or more asymmetric carbon atoms. Any stereoisomers based on the asymmetric carbon atom(s) such as optically active isomers and diastereo isomers, any mixture of the stereo isomers, racemates and the like fall within the scope of the present invention. Furthermore, the compound represented by formula (I) may exist as an acid addition salt or a base addition salt, which also falling within the scope of the present invention. Examples of the acid addition salt include, for example, a mineral acid salt such as hydrochloride, sulfate, and nitrate, and an organic acid salt such as p-toluene sulfonate and maleate. Examples of the base addition salt include, for example, a metal salt such as sodium salt, potassium salt, and calcium salt, ammonium salt, and an organic amine salt such

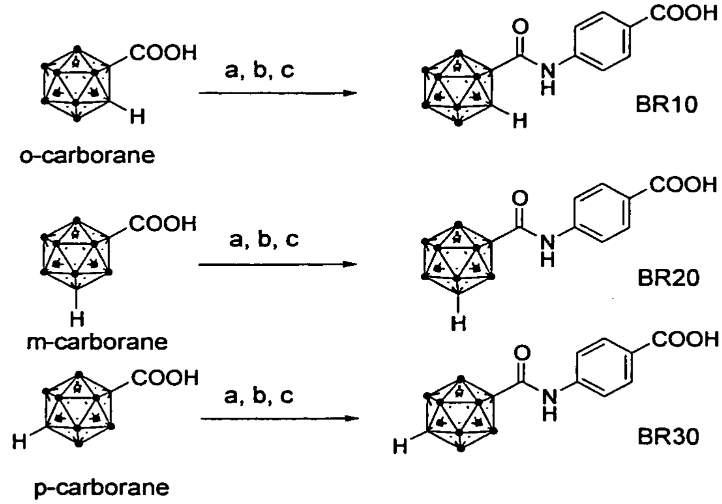
as triethylamine salt. In addition, an amino acid salt such as glycine salt as well as an internal salt (a zwitterion) fall within the scope of the present invention. Moreover, the compound or a salt thereof according to the present invention may form a hydrate or a solvate, and any of these substances fall within the scope of the present invention.

[0025]

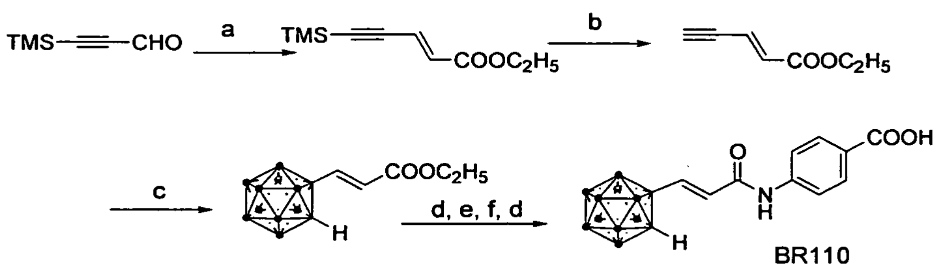
Preparations of typical compounds encompassed within formula (I) are shown in the following schemes. In addition, preparations of these compounds are also described in detail and specifically in the examples of the specification. Those ordinary skilled in the art can prepare any compounds falling within the scope of general formula (I) by referring to the preparations described in the following scheme and specific explanation in the examples, appropriately choosing starting materials, reaction conditions, reagents and the like, and optionally applying modifications or alterations thereto. In the formula (I), compounds wherein X is a single bond, R^1 is unsubstituted dicarba-*closo*-dodecaboran-yl group, and R^2 is a hydroxyl group (the compounds indicated as BE100, 200, and 300 in the following schemes ; J. Chem. Soc. Dalton Trans., pp.401-411, 1998; Zh. Obshch. Khim., 41, pp.1516-20, 1971) ; and compound wherein X is a single bond, R^1 is 12-(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaboran-yl group, and R^2 is a hydroxyl group (the compound indicated as BE160 ; J. Chem. Soc. Dalton Trans., pp.401-411, 1998) can be prepared by the methods described in the literature.

[0026]

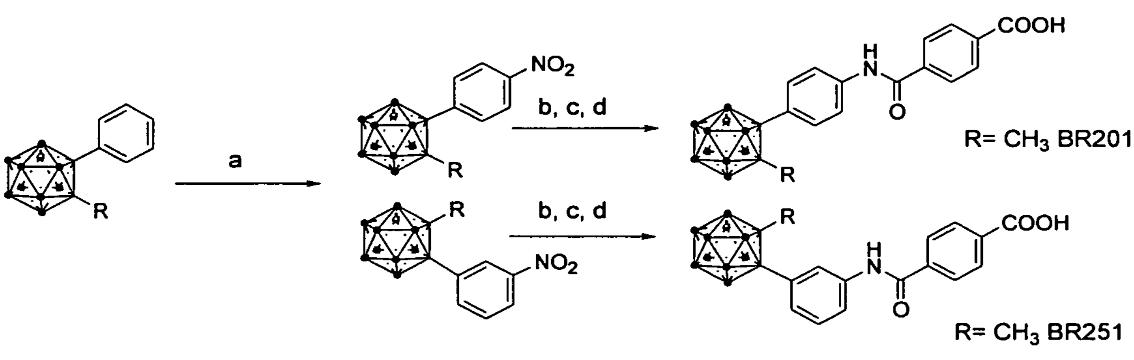
[Formula 10]



a) $(COCl)_2$, DMF/ CH_2Cl_2; b) methyl 4-aminobenzoate, DMAP/ CH_2Cl_2; c) KOH/ H_2O-THF



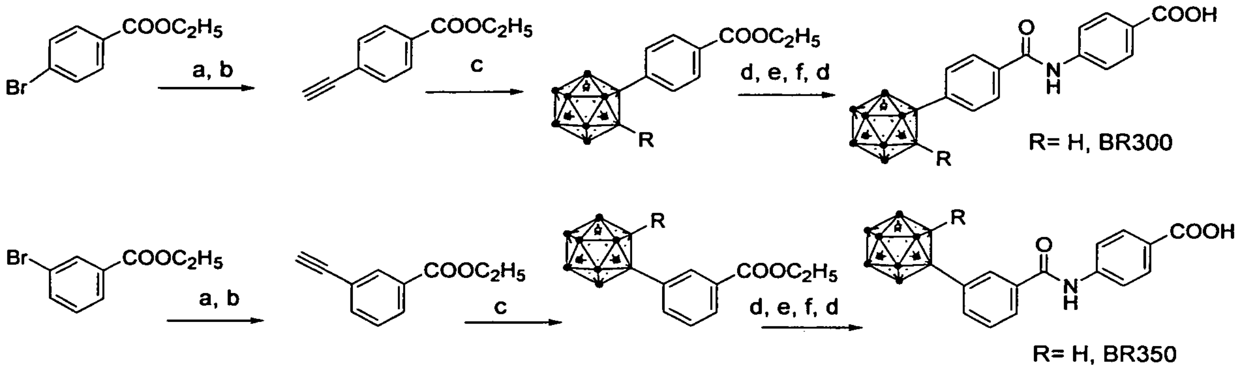
a) $(EtO)_2POCH_2COOEt$, NaH/ THF; b) K_2CO_3/ EtOH; c) cecaborane (14) / CH_3CN-C_6H_6;
d) KOH/ H_2O-THF; e) (COCl)2, DMF (cat)/ CH_2Cl_2; f) methyl 4-aminobenzoate/ pyridine



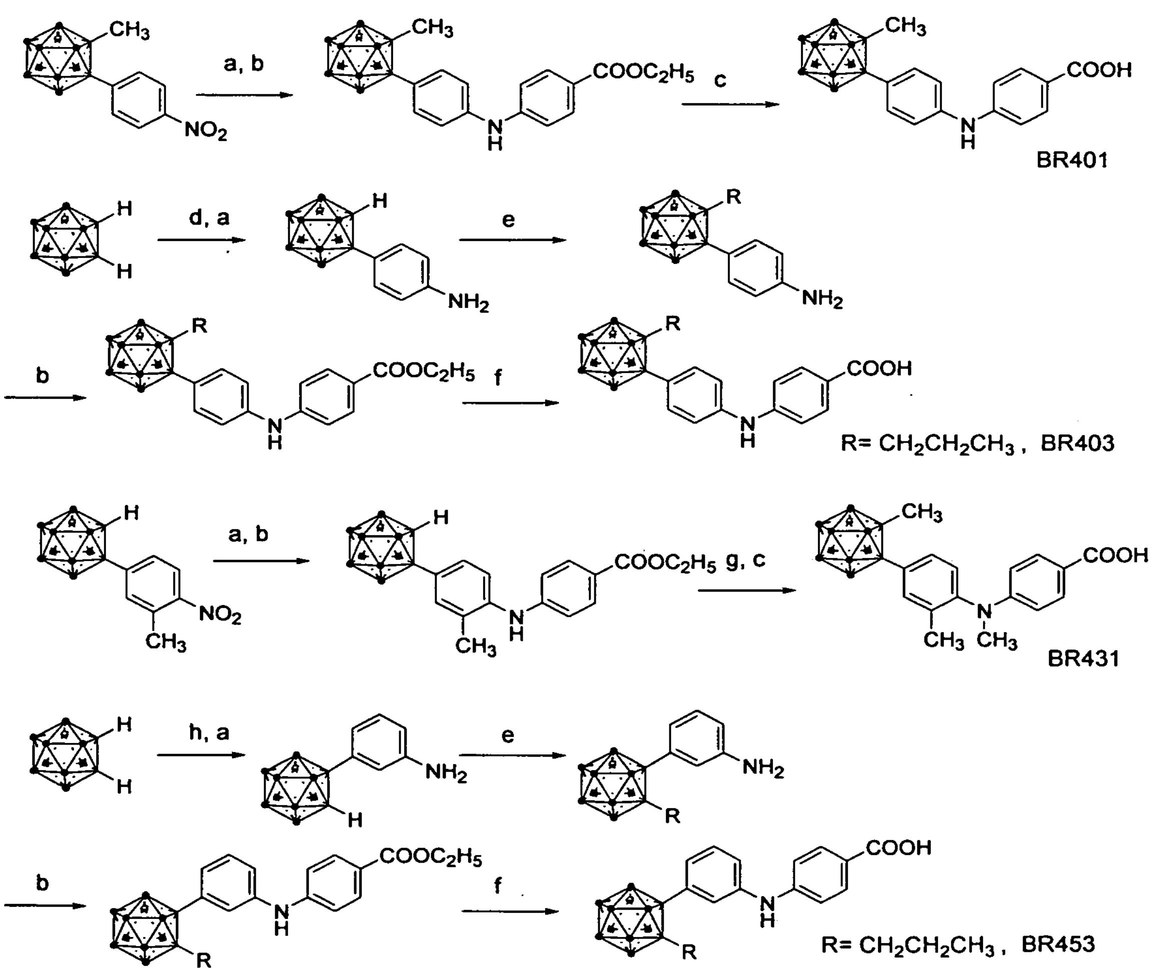
a) HNO_3, H_2SO_4/ CH_2Cl_2; b) H_2, Pd-C/ EtOH; c) terephtalic acid monomethyl ester chloride/ pyridine;
d) KOH/ H_2O-THF

[0027]

[Formula 11]



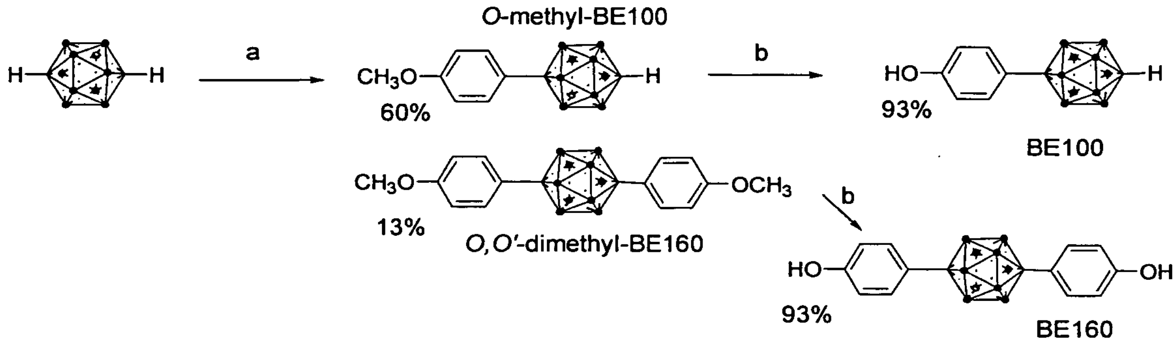
a) ethynyltrimehylsilane, $(PPh_3)_2PdCl_2$, CuI, iPrNH. THF; b) K_2CO_3/ EtOH; c) decaborane (14)/ $CH_3CN-C_6H_6$; d) KOH/ H_2O-THF; e) (COCl)2, DMF (cat)/ CH_2Cl_2; f) methyl 4-aminobenzoate/ pyridine



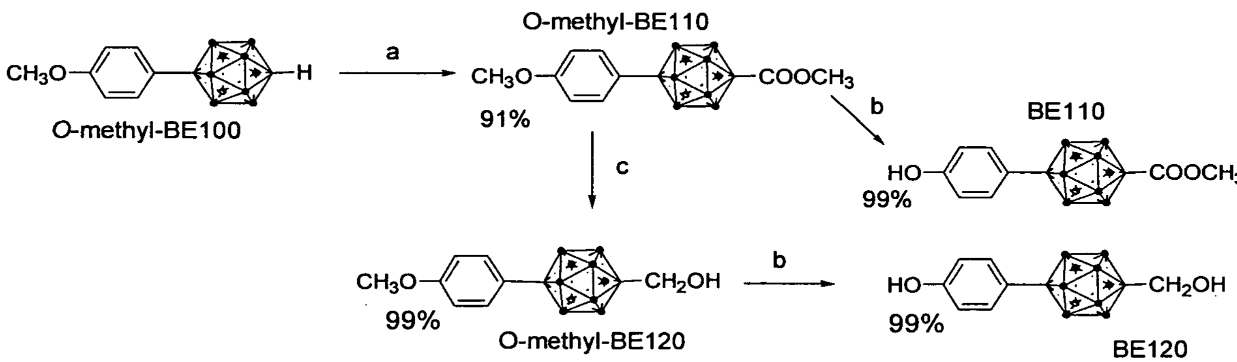
a) H_2, Pd-C/ EtOH; c) ethyl p-iodobenzoate, Cs_2CO_3, $Pd_2(dba)_3$, BINAP/ toluene; c) KOH/ H_2O-THF; d) 1)*n*-BuLi, CuCl/ DME, 2) 4-nitroiodobenzene/ pyridine; e) NaH, R-I/ DMF; f) ; g) NaH, CH_3I/ DMF; h) 1)*n*-BuLi, CuCl/ DME, 2) 3-nitroiodobenzene/ pyridine

[0028]

[Formula 12]



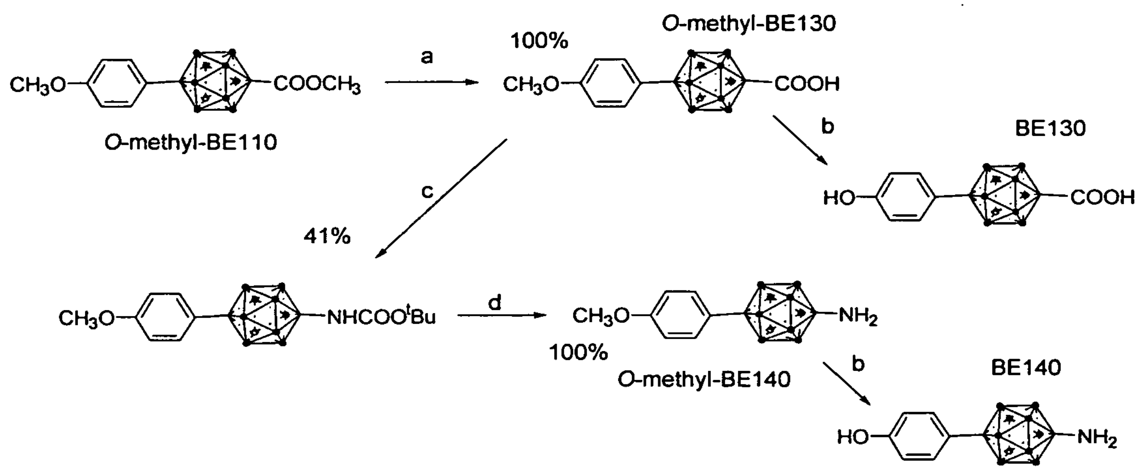
a) 1) n-BuLi, CuCl/DME 2) p-iodoanisole/ pyridine, reflux b) BBr_3/ CH_2Cl_2



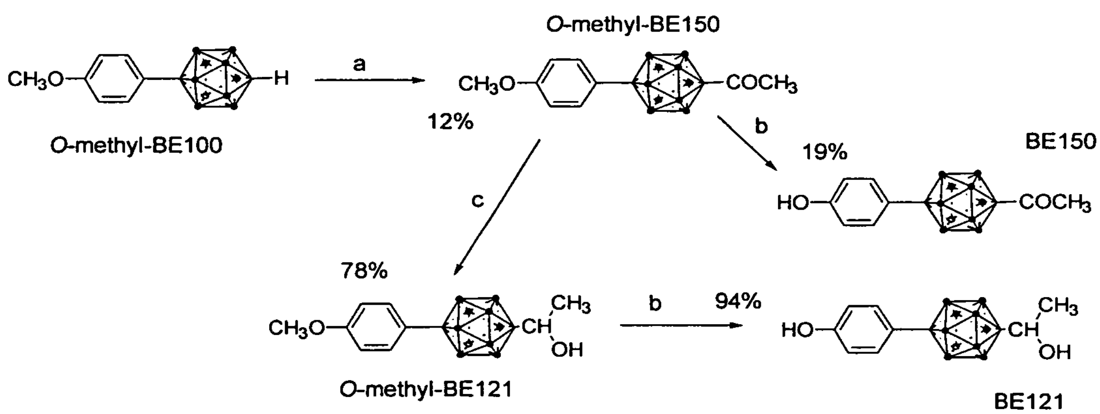
a) 1) n-BuLi/ benzene-Et_2O 2) $ClCOOCH_3$ b) BBr_3/ CH_2Cl_2 c) $LiAlH_4$/ THF

[0029]

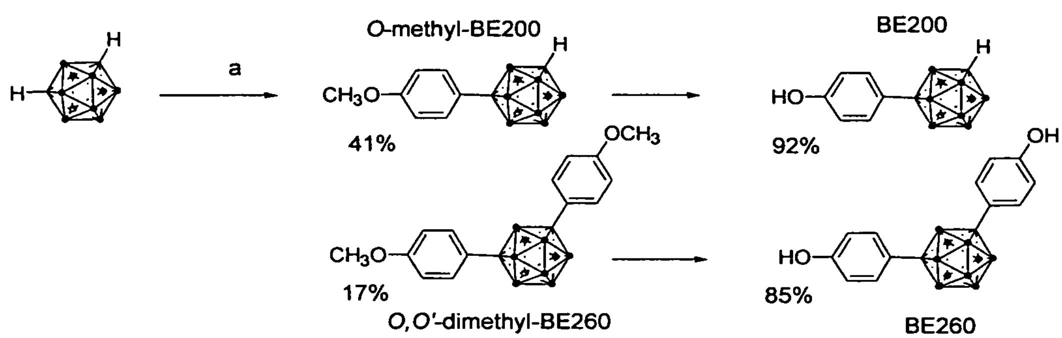
[Formula 13]



a) KOH/ H_2O-THF b) BBr_3/ CH_2Cl_2 c) DPPA, Et_3N, DMAP/ t-BuOH reflux d) CF_3COOH/ CH2Cl2



a) 1) n-BuLi/ Et_2O 2) CH_3COCl/ THF b) BBr_3/ CH_2Cl_2 c) $NaBH_4$, EtOH



a) 1) n-BuLi, CuCl/DME 2) p-iodoanisole/ pyridine, reflux b) BBr_3/ CH_2Cl_2

[0030]

The compounds represented by formula (I) have an action as a ligand of a nuclear receptor (a retinoic acid receptor) to specifically regulate transcriptional activation by the retinoic acid receptor. More specifically, the compounds have affinity to retinoic acid receptor RAR or retinoic acid receptor RXR, and can function as an agonist or an antagonist for these receptors. Some of the compounds have an action of enhancing activities of retinoic acid. On the basis of these functions, the compounds represented by formula (I) can prevent proliferation of leukemia cells and promote differentiation to normal cells. Therefore, the compounds are useful as a medicaments for therapeutic treatment of leukemia by differentiation inducing therapy, and also useful for therapeutic and/or preventive treatment of cancer, rheumatism, arteriosclerosis, diabetes, rejection reaction due to organ transplantation, and graft versus host disease. Moreover, they can be used as medicament for ^{10}B-Neutron Capture Therapy based on targeting to cancer cells utilizing the affinity to the nuclear receptor. Furthermore, they can be used as estrogenic agents.

[0031]

As the active ingredient of the medicament of the present invention, the compound represented by the aforementioned formula (I) or a physiologically acceptable salt thereof, a hydrate thereof or a solvate thereof can be used. As the medicament of the present invention, the aforementioned active ingredient, per se, may be administered. However, generally it is desirable that a pharmaceutical composition is formulated which comprises the aforementioned active ingredient and one or more pharmaceutical additives and then administered. The route of administration of the medicament of the present invention is not limited. The medicament can be administered orally or parenterally.

[0032]

Examples of the pharmaceutical compositions suitable for oral administrations include tablets, capsules, powders, subtilized granules, granules, liquids, syrups and the like. Examples of the pharmaceutical compositions suitable for parenteral administrations include injections, drip infusions, suppositories, inhalants, eye drops, nasal drops, transdermally-adsorbable formulation, ointments, creams, patches and the like. Examples of pharmaceutical additives include

excipients, disintegrators or disintegrating aids, binders, lubricants, coating agents, colorants, diluents, base materials, dissolving agents or solubilizers, isotonic agents, pH modifiers, stabilizers, propellants, adhesives and the like. Appropriate additives can be chosen and used depending on the type of the pharmaceutical composition. The doses of the medicament of the present invention are not particularly limited, and suitable doses can appropriately be chosen depending on the conditions such as the kind of the compound as an active ingredient, a purpose of preventive or therapeutic treatment, the type of a disease, the age and symptoms of a patient, the route of administration and the like.

[0033]

Examples

The present invention will be more specifically explained by referring to the following examples. However, the scope of the present invention is not limited to these examples. The compound numbers in the examples correspond to those in the schemes shown above.

[0034]

Example 1

1,2-dicarba-*closo*-dodecaborane-1-carboxylic acid (100 mg, 0.531mmol) was dissolved in dichloromethane (1 ml), and oxalyl chloride (101 mg, 0.795mmol) and catalytic amount of dimethyl formamide (DMF , one drop) were added, and the mixture was stirred at room temperature for 3h. Then the reaction mixture was concentrated. The residue and methyl 4-aminobenzoate (80.3 mg, 0.531mmol) were suspended in dichloromethane (2ml), 4-dimethylaminopyridine (130 mg, 1.06mmol) was added at 0℃, stirred at room temperature for 1h under argon atmosphere. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with dichloromethane. The organic layer was washed with water, saturated sodium hydrogencarbonate solution, water, and brine in order, and dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent: hexane/ethylacetate=5/1) to give methyl 4-[(1,2-dicarba-*closo*-dodecaboran-1-yl)carbamoyl]benzoate (58 %).

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, m), 3.92 (3H, s), 4.35 (1H, br s), 7.55 (2H, d, J = 8.8 Hz), 7.71 (1H, br s), 8.06 (2H, d, J = 8.8 Hz).

[0035]

4-[(1,2-dicarba-*closo*-dodecaboran-1-yl)carbamoyl]methyl benzoate (73 mg, 0.227mmol) was dissolved in tetrahydrofuran (THF)(1 ml), 1N potassium hydroxide (0.91ml) was added, and the mixture was stirred at room temperature for 16 h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. The reaction mixture was purified by silica gel flash column chromatography to give BR10 (60%).

BR10 : colorless needles (ethyl acetate/dichloromethane)

m.p. : 249-251℃

^{1}H-NMR ($CDCl_3$) δ :1.00-3.30 (10H, br m), 4.36 (1H, br s), 7.59 (2H, d, J = 8.8 Hz), 7.75 (1H, br s), 8.12 (2H, d, J = 8.8 Hz)

Anal. Calcd for $C_{10}H_{17}B_{10}NO_3$: C, 39.08; H, 5.57; N 4.56. Found C, 39.13; H, 5.58; N, 4.44.

[0036]

BR20 was synthesized from1,7-dicarba-*closo*-dodecaborane-1-carboxylic acid by the same method as preparation of BR10.

BR20: colorless needles (ethyl acetate / dichloromethane)

m.p. : 271-273℃; ^{1}H-NMR (DMSO-d_6) δ :1.30-3.20 (10H, br m), 4.30 (1H, br s), 7.69 (2H, d, J = 8.8 Hz), 7.89 (2H, d, J = 8.8 Hz), 9.74 (1H, s), 12.87 (1H, br s).

[0037]

BR30 was synthesized from 1,12-dicarba-*closo*-dodecarorane-1-carboxylic acid by the same method as preparation of BR10.

BR30 : Colorless needles (ethyl acetate / hexane); m.p. : > 300℃;

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 3.94 (1H, br s), 7.61 (2H, d, J = 8.8 Hz), 7.86 (2H, d, J = 8.8 Hz), 9.36 (1H, s), 12.80 (1H, br s).

[0038]

Example 2

Ethynyltrimethylsilane (5.0 g, 50.9 mmol) was dissolved in dry diethyl ether (50 ml), 1.6 M n-butyllithium in hexane(35.0 ml, 56.0 mmol) was added dropwise at 0℃ under argon atmosphere. The mixture was stirred at the same temperature for 1h. DMF(3.72g, 50.9mmol) was dissolved in diethyl ether (20ml), and was added dropwise

below 5℃ for 30 min, then the mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with diethyl ether. The organic layer was washed with water, saturated sodium hydrogencarbonate solution, and brine in order, and dried over sodium sulfate. Purification by distillation (40-45℃/15mmHg) gave 3-(trimethylsilyl)propiol aldehyde (28%).

Colorless oil

^{1}H-NMR ($CDCl_3$) δ :0.27 (9H, s), 9.17 (1H, s).

[0039]

To a suspension of sodium hydride (556 mg, 13.9mmol) in THF (7 ml), diethyl phosphonoethyl acetate (3.12g, 13.9 mmol) in THF (7ml) was added dropwise under argon atmosphere. The mixture was stirred at room temperature for 30 min, then 3-(trimethylsilyl) propiolaldehyde in THF(7 ml) was added dropwise at 0℃. The mixture was stirred at room temperature for 1.5h, then poured into ice water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane→hexane/ethyl acetate=50/1) to give ethyl 5-trimethylsilyl-(E)-2 -penten-4-ynoate(65%).

Colorless oil

^{1}H-NMR ($CDCl_3$) δ :0.21 (9H, s), 1.29 (3H, t, J = 7.2 Hz), 4.21 (2H, q, J = 7.2 Hz), 6.24 (1H, d, J = 15.9 Hz), 6.74 (1H, d, J = 15.9 Hz).

[0040]

Potassium carbonate (563mg, 4.07mmol) was added to a solution of ethyl 5-trimethylsilyl-(E)-2-penten-4-ynoate(800mg, 4.07mmol) in ethanol (10 ml), and the mixture was stirred at room temperature for 1h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography to give ethyl (E)-2-penten-4-ynoate (79%).

Colorless oily substance

^{1}H-NMR ($CDCl_3$) δ :1.30 (3H, t, J = 7.1 Hz), 3.34 (1H, dd, J = 0.7, 2.4 Hz), 4.23 (2H, q, J = 7.1 Hz), 6.32 (1H, dd, J = 0.7, 15.9 Hz), 6.72 (1H, dd, J = 2.4, 15.9 Hz).

[0041]

A mixture of ethyl (E)-2-penten-4-ynoate(360mg, 2.90mmol) and decaborane (14) (532 mg, 4.35 mmol) in acetonitrile (1.5 ml) and benzene (15 ml) was refluxed for 17h under argon atmosphere. After the mixture was concentrated, it was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=10/1) to give 3-(1,2-dicarba-*closo*- dodecaboran-1-yl)-(E)-ethyl acrylate (64%).

Colorless prisms (hexane)

m.p. : 68-69℃

^{1}H-NMR ($CDCl_3$) δ :1.30 (3H, t, J = 7.1 Hz), 1.50-3.40 (10H, br m), 3.69 (1H, br s), 4.22 (2H, q, J = 7.1 Hz), 6.20 (1H, d, J = 15.4 Hz), 6.84 (1H, d, J = 15.4 Hz)

Anal. Calcd for $C_7H_{18}B_{10}O_2$: C, 34.70; H, 7.49. Found C, 34.41; H, 7.66.

[0042]

To a solution of 3-(1,2-dicarba-*closo*-dodecaboran-1-yl)-(E)-ethyl acrylate (220 mg, 0.908 mmol) in THF(5 ml), 1N potassium hydroxide (1.82 ml) was added, and the mixture was stirred at room temperature for 7h. The reaction was quenched by the addition of 2N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : chloroform/methanol= 10/1) to give 3-(1,2-dicarba-*closo*-dodecaboran-1-yl) -(E)-propenoic acid (74%).

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 5.47 (1H, br s), 6.22 (1H, d, J = 15.4 Hz), 6.92 (1H, d, 15.4 Hz), 13.00 (1H, br).

[0043]

The propenoic acid (60 mg, 0.28 mmol) obtained above was dissolved in dichloromethane (1 ml), oxalyl chloride (53.3 mg, 0.42 mmol) and catalytic amount of DMF(one drop) were added. The mixture was stirred at room temperature for 1h, and was concentrated. The residue was dissolved in pyridine (1 ml), and 4-amino methylbenzoate (46.6 mg, 0.308 mmol) was added. After stirring at room temperature for 18h, the reaction was quenched by the addition of 2N hydrochloric acid, the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated sodium hydrogencarbonate solution, water, and brine in order, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=5/1) to give methyl

4-[2-(1,2-dicarba-*closo*-decaborane-1-yl)-(E)-ethenylcarboxamine]benzoate (44%).

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, m), 3.72 (1H, br s), 3.91 (3H, s), 6.37 (1H, d, J = 15.0 Hz), 6.96 (1H, d, J = 15.0 Hz), 7.40 (1H, br s), 7.64 (2H, d, J = 8.8 Hz), 8.04 (2H, d, J = 8.8 Hz)

HRMS Calcd for $C_{13}H_{21}B_{10}NO_3$ 347.2524, Found 347.2534

[0044]

The methyl benzoate (36mg, 0.104 mmol) obtained above was dissolved in THF(1ml), 1N potassium hydroxide(0.468 ml) was added, and stirred at room temperature for 36h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, and then with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : chloroform/methanol=50/1→5/1) to give 4-[2-(1,2-dicarba-*closo*-dododecaboran-1-yl)-(E)-ethenylcarboxamide] benzoic acid (BR110) (39%).

Colorless needles (ethyl acetate/hexane)

m.p. : > 300℃; ^{1}H-NMR ($CDCl_3$) δ :1.40-3.20 (10H, br m), 5.50 (1H, br s), 6.67 (1H, d, J = 15.1 Hz), 6.98 (1H, d, J = 15.1 Hz), 7.73 (2H, d, J = 8.8 Hz), 7.92 (2H, d, J = 8.8 Hz), 10.62 (1H, s), 12.75 (1H, br)

HRMS Calcd for $C_{12}H_{19}B_{10}NO_3$ 333.2368, Found 333.2367

[0045]

Example 3

A mixture of ethenylbenzene (5.51g, 53.9 mmol) and decaborane (14)(2.64g, 21.6 mmol) in acetonitrile (5.5 ml) and benzene (55 ml) was refluxed for 4 days under argon atmosphere. Then the mixture was concentrated, it was purified by silica gel column chromatography (eluent : hexane) to give 1-phenyl-1,2-dicarba-*closo*-dodecaborane(74%).

Colorless prisms (hexane)

m.p. : 66-67℃

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, br m), 3.97 (1H, br s), 7.33 (2H, m), 7.39 (1H, m), 7.49 (2H, m).

[0046]

1-Phenyl-1,2-dicarba-*closo*-dodecaborane(950mg, 4.31 mmol) was dissolved in

dry diethylether (15 ml), 1.54M n-butyl lithium in hexane solution(2.8ml, 4.31 mmol) was added dropwise at 0℃ under argon atmosphere. After the mixture was stirred at room temperature for 3h, it was cooled to −78℃. Methyl iodide (673mg, 4.74 mmol) in THF(3 ml) was added dropwise, and further stirred at room temperature for 16h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with diethylether. The organic layer was washed with water, and then with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography(eluent : hexane) to give 1-methyl-2-phenyl-1,2-dicarba-*closo*-dodecaborane(94%).

Colorless prisms (hexane)

m.p. : 102-103℃

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, br m), 1.69 (3H, s), 7.39 (2H, m), 7.45 (1H, m), 7.65 (2H, m)

HRMS Calcd for $C_9H_{18}B_{10}$ 234.2412, Found 234.2422

[0047]

A solution of 1-methyl-2-phenyl-1,2-dicarba-*closo*-dodecaborane(900 mg, 3.84mmol) in dichloromethane (17.5 ml) was added dropwise to a mixture of concentrated nitric acid and concentrated sulfuric acid (15:85, v/v, 17.5 ml) at 0℃, and stirred at room temperature for 4 h. The mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=30/1) to give 4-(2-methyl-1,2-dicarba-*closo*- dodecaboran-1-yl)nitrobenzene(a)(34%) and 3-(2-methyl-1,2-dicarba-*closo* -dodecaboran-1-yl)nitrobenzene(b)(57%).

[0048]

(a) colorless prisms (ethyl acetate/hexane)

m.p. : 105-106℃

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, br m), 1.73 (3H, s), 7.87 (2H, d, J = 9.0 Hz), 8.26 (2H, d, J = 9.0 Hz)

HRMS Calcd for $C_9H_{17}B_{10}NO_2$ 279.2262, Found 279.2264

(b) colorless prisms (ethyl acetate/hexane)

m.p. : 126-127℃

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, br m), 1.74 (3H, s), 7.64 (1H, t, J = 8.1 Hz), 8.01 (1H, ddd, J = 1.1, 2.0, 8.1 Hz), 8.34 (1H, ddd, J = 1.1, 2.0, 8.1 Hz), 8.53 (1H, t, J = 2.0 Hz)

HRMS Calcd for $C_9H_{17}B_{10}NO_2$ 279.2262, Found 279.2243

[0049]

4-(2-Methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene (349 mg, 1.25 mmol) was dissolved in ethanol (25 ml), and was hydrogenated at room temperature for 1 h using 10% Pd/C(87 mg) under the atmospheric pressure of hydrogen. After removal of catalyst by filtration, the filtrate was concentrated to give 4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)aniline (95%).

^{1}H-NMR ($CDCl_3$) δ :1.40-3.50 (10H, br m), 1.68 (3H, s), 4.01 (2H, br), 6.62 (2H, d, J = 8.6 Hz), 7.39 (2H, d, J = 8.6 Hz).

[0050]

The amine obtained above (100 mg, 0.401 mmol) was dissolved in pyridine (2.5 ml), terephthalic acid monomethyl ester chloride (119 mg, 0.599 mmol) was added at 0℃, and stirred at room temperature for 3h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated sodium hydrogen carbonate solution, water, and brine in order, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : dichloromethane /hexane = 3/2→2/1) to give methyl 4-[4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylcarbamoyl]benzoate (96%).

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, br m), 1.71 (3H, s), 3.97 (3H, s), 7.66 (2H, d, J = 9.2 Hz), 7.70 (2H, d, J = 9.2 Hz), 7.91 (1H, br s), 7.93 (2H, d, J = 8.6 Hz), 8.18 (2H, d, J = 8.6 Hz).

[0051]

The methyl benzoate obtained above (140 mg, 0.34 mmol) was dissolved in THF (2 ml), 1N potassium hydroxide (0.68 ml) was added, and stirred at room temperature for 14 h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent :

chloroform/methanol=5/1) to give 4-[4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)-phenylcarbamoyl]benzoic acid (BR201)(98%).

Colorless needles (ethyl acetate/hexane)

m.p. : > 300℃

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 1.74 (3H, s), 7.71 (2H, d, J = 8.8 Hz), 7.91 (2H, d, J = 8.8 Hz), 8.04 (2H, d, J = 8.6 Hz), 8.08 (2H, d, J = 8.6 Hz), 10.66 (1H, s), 13.32 (1H, br)

Anal. Calcd for $C_{17}H_{23}B_{10}NO_3$: C, 51.37; H, 5.83; N, 3.52. Found C, 51.13; H, 5.68; N, 3.37.

[0052]

3-(2-Methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene was converted to 4-[3-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylcarbamoyl]benzoic acid (BR251) employing the method described above.

Colorless needles (ethyl acetate/hexane)

m.p. : 284-286℃

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 1.77 (3H, s), 7.45 (1H, br d, J = 8.2 Hz), 7.49 (1H, t, J = 8.2 Hz), 8.05 (1H, br d, J = 8.2 Hz), 8.06 (2H, d, J = 8.6 Hz), 8.09 (2H, d, J = 8.6 Hz), 8.25 (1H, br s), 10.61 (1H, s), 13.30 (1H, br)

HRMS Calcd for $C_{17}H_{23}B_{10}NO_3$ 397.2681, Found 397.2683

Anal. Calcd for $C_{17}H_{23}B_{10}NO_3$/0.2 H_2O: C, 50.91; H, 5.88; N, 3.49. Found C, 50.71; H, 5.97; N, 3.36.

[0053]

Example 4

A mixture of ethyl 4-bromobenzoate (1.5 g, 6.55 mmol), ethynyl trimethylsilane (965 mg, 9.82 mmol), diisopropylamine (1.39 g, 13.7 mmol), cuprous iodide(25mg, 0.131mmol), and bis(triphenylphosphine) palladium(II) chloride (184 mg, 0.262 mmol) was heated at 45℃ for 4 h in dry THF (10 ml) under argon atmosphere. The reaction was quenched by the addition of water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=100/1) to give ethyl 4-[(trimethylsilyl)ethynyl]benzoate (73%).

^{1}H-NMR ($CDCl_3$) δ :0.26 (9H, s), 1.39 (3H, t, J = 7.2 Hz), 4.37 (2H, q, J = 7.2 Hz), 7.51 (2H, d, J = 8.6 Hz), 7.97 (2H, d, J = 8.6 Hz).

[0054]

4-[(Trimethylsilyl)ethynyl]ethyl benzoate (1.15 g, 4.67 mmol) was dissolved in THF (10 ml), 1M tetrabutylammonium fluoride/THF solution (5.14 ml) was added dropwise at 0℃. After stirring at room temperature for 30 min, the reaction was quenched by the addition of water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=20/1) to give 4-ethynylethylbenzoate(40%).

Colorless oily substance

^{1}H-NMR ($CDCl_3$) δ :1.40 (3H, t, J = 7.1 Hz), 3.23 (1H, s), 4.38 (2H, q, J = 7.1 Hz), 7.55 (2H, d, J = 8.2 Hz), 8.00 (2H, d, J = 8.2 Hz).

[0055]

A mixture of 4-ethynyl ethyl benzoate(320 mg, 1.84 mmol) and decaborane(14) (337 mg, 2.76 mmol) was refluxed for 3 days in acetonitrile (1 ml) and benzene (15 ml) under argon atmosphere,. The mixture was concentrated and purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=15/1) to give ethyl 4-(1,2-dicarba-*closo* -dodecaboran-1-yl)benzoate (71%).

Colorless flakes (ethanol)

m.p. : 111-112℃

^{1}H-NMR ($CDCl_3$) δ :1.39 (3H, t, J = 7.1 Hz), 1.50-3.50 (10H, br m), 4.01 (1H, br s), 4.39 (2H, q, J = 7.1 Hz), 7.54 (2H, d, J = 8.8 Hz), 8.00 (2H, d, J = 8.8 Hz)

HRMS Calcd for $C_{11}H_{20}B_{10}O_2$ 292.2466, Found 292.2487

[0056]

Ethyl 4-(1,2-dicarba-*closo*-dodecaboran-1-yl) benzoate (374 mg, 1.28 mmol) was dissolved in THF (5 ml), 1N potassium hydroxide (3.84 ml) was added, and stirred at room temperature for 15h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated. The remaining crystals were washed with hexane to give 4-(1,2-dicarba-*closo*-dodecaboran-1-yl)benzoic acid.

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 5.88 (1H, br s), 7.72 (2H, d, J = 8.5 Hz), 7.94 (2H, d, 8.5 Hz), 13.29 (1H, br).

[0057]

The benzoic acid obtained above (140 mg, 0.53 mmol) was suspended in dichloromethane (1.51 ml), oxalyl chloride (202 mg, 1.59 mmol) and catalytic amount of DMF(1 drop) were added. After stirring at room temperature for 1h, the mixture was concentrated. The residue was dissolved in pyridine (1.5 ml), and methyl 4-aminobenzoate (84.0 mg, 0.556 mmol) was added. After stirring at room temperature for 15h, the reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated sodium hydrogencarbonate solution, water, and brine in order, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=3/1) to give methyl 4-{[4-(1,2-dicarba-*closo*-dodecaboran-1-yl)phenyl]carboxamide}benzoate (48%).

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, m), 3.92 (3H, s), 4.02 (1H, br s), 7.62 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.8 Hz), 7.84 (2H, d, J = 8.4 Hz), 7.89 (1H, br s), 8.07 (2H, d, J = 8.8 Hz).

[0058]

The methyl benzoate obtained above (94 mg, 0.236 mmol) was dissolved in THF(3 ml), 1N potassium hydroxide (1.18 ml) was added, and stirred at 40℃ for 16h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : chloroform/methanol=5/1) to give 4-{[4-(1,2-dicarba-*closo*-dodecaboran-1-yl)phenyl]carboxamide}benzoic acid (BR300)(41%).

Colorless needles (ethyl acetate)

m.p. : > 300℃

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 5.92 (1H, br s), 7.76 (2H, d, J = 8.8 Hz), 7.88 (2H, d, J = 8.8 Hz), 7.94 (2H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.8 Hz), 10.61 (1H, s), 12.80 (1H, br)

Anal. Calcd for $C_{16}H_{21}B_{10}NO_3$: C, 50.12; H, 5.52; N, 3.65. Found C, 50.18; H, 5.80; N,

3.41.

[0059]

A mixture of ethyl 3-bromobenzoate (1.0 g, 4.37 mmol), ethynyl trimethylsilane (644 mg, 6.56 mmol), diisopropylamine (929 mg, 9.20 mmol), cuprous iodide(I) (16.6 mg, 0.0872 mmol), and bis(triphenylphosphine) palladium(II) chloride (123 mg, 0.175 mmol) was heated at 45℃ for 5h in dried THF (8 ml) under argon atmosphere. After cooling, the reaction was quenched by the addition of water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=50/1) to give ethyl 3-[(trimethylsilyl)-ethynyl]benzoate (90%)

^{1}H-NMR ($CDCl_3$) δ :0.26 (9H, s), 1.40 (3H, t, J = 7.1 Hz), 4.38 (2H, q, J = 7.1 Hz), 7.38 (1H, dd, J = 7.3, 8.3 Hz), 7.63 (1H, d, J = 7.3 Hz), 7.98 (1H, d, J = 8.3 Hz), 8.13 (1H, s).

[0060]

Potassium carbonate (583 mg, 4.22 mmol) was added to an ethanol solution (10 ml) of ethyl 3-[(trimethylsilyl)ethynyl]benzoate (1.04 g, 4.22 mmol), and stirred at room temperature for 2h. The mixture was concentrated, and the residue was dissolved in ethyl acetate. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=30/1) to give ethyl 3-ethynylbenzoate (96%).

Colorless needles

m.p. : 36-37℃

^{1}H-NMR ($CDCl_3$) δ :1.40 (3H, t, J = 7.1 Hz), 3.12 (1H, s), 4.34 (2H, q, J = 7.1 Hz), 7.41 (1H, t, J = 7.8 Hz), 7.66 (1H, dt, J = 7.8, 1.5 Hz), 8.03 (1H, dt, J = 7.8, 1.5 Hz), 8.17 (1H, t, J = 1.5 Hz).

[0061]

Ethyl 3-ethynyl benzoate was reacted with decaborane(14) and converted to ethyl 3-(1,2-dicarba-*closo*-dodecaboran-1-yl)benzoate similar to the case of ethyl 4-(1,2-dicarba-*closo*-dodecaboran-1-yl)benzoate. The yield of the product was 68%.

Colorless flakes (ethanol)

m.p. : 168-169℃

^{1}H-NMR ($CDCl_3$) δ :1.41 (3H, t, J = 7.7 Hz), 1.50-3.50 (10H, m), 4.04 (1H, br s), 4.40 (2H, q, J = 7.1 Hz), 7.43 (1H, t, J = 7.7 Hz), 7.70 (1H, ddd, J = 1.1, 2.2, 7.7 Hz), 8.07 (1H, dt, J = 7.7, 1.1 Hz), 8.10 (1H, t. J = 1.7 Hz)

HRMS Calcd for $C_{11}H_{20}B_{10}O_2$ 292.2466, Found 292.2474

[0062]

4-[[3-(1,2-Dicarba-*closo*-dodecaboran-1-yl)phenyl]carboxamide]benzoic acid was prepared from 3-(1,2-dicarba-*closo*-dodecaboran-1-yl)ethylbenzoate (BR351) by the same procedure that used for BR300.

Colorless needles (ethyl acetate/hexane)

m.p. : 236-239℃

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 5.89 (1H, br s), 7.60 (1H, t, J = 8.0 Hz), 7.82 (1H, br d, J = 8.0 Hz), 7.86 (2H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.8 Hz), 8.04 (1H, br d, J = 8.0 Hz), 8.05 (1H, br s), 10.61 (1H, s), 12.89 (1H, br)

HRMS Calcd for $C_{16}H_{21}B_{10}NO_3$ 383.2524, Found 383.2542

Anal. Calcd for $C_{16}H_{21}B_{10}NO_3$/0.5 H_2O: C, 48.97; H, 5.65; N, 3.57. Found C, 48.99; H, 5.83; N, 3.49.

[0063]

Example 5

1.54M n-Butyl lithium/hexane solution (37.8 ml, 58.2 mmol) was added dropwise to DME solution (100 ml) of 1,2-dicarba-*closo*-dodecaborane (4.0 g, 27.7 mmol) at 0℃ under argon atmosphere. The mixture was stirred at room temperature for 30 min, cuprous chloride (7.13 g, 72.0 mmol) was added in one portion, and further stirred at room temperature for 2h. After the treatment, pyridine (16.7 ml, 208 mmol) was added, then 4-iodonitrobenzene (8.28 g, 33.3 mmol) was added at one time, and heated at 100℃ for 22h. After cooling, the mixture was diluted with diethyl ether, stirred at room temperature for 12h, and the insoluble substance was separated and filtered with Celite. The filtrate was washed with 2N hydrochloric acid, water, and brine in order, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : n-hexane/ethyl acetate=7/1) to give 4-(1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene (75%).

Colorless prism (ethyl acetate/hexane)

m.p. : 170-172℃

^1H-NMR ($CDCl_3$) δ 1.50-3.50 (10H, br m), 4.02 (1H, br s), 7.67 (2H, d, J = 9.2 Hz), 8.21 (2H, d, J = 9.2 Hz)

[0064]

4-(1,2-Dicarba-*closo*-dodecaboran-1-yl) nitrobenzene (5.45 g, 20.5 mmol) in ethanol (220 ml) was hydrogenated at room temperature for 3h under the atmospheric pressure of hydrogen using 10% Pd/C (1.36 g). After removal of catalyst by filtration, the filtrate was concentrated, and 4-(1,2-dicarba-*closo*-dodecaboran-1-yl)aniline was obtained (85%).

^1H-NMR ($CDCl_3$) δ 1.50-3.50 (10H, br m), 3.83 (3H, br), 6.56 (2H, d, J = 9.2 Hz), 7.27 (2H, d, J = 9.2 Hz)

[0065]

Sodium hydride (40.8 mg, 1.02 mmol) was suspended in DMF (1 ml), and a solution of 4-(1,2-dicarba-*closo*-dodecaboran-1-yl) aniline (200 mg, 0.850 mmol) in DMF (3 ml) was added to the suspension. The mixture was stirred at room temperature for 5 min, 1-indopropane (217 mg, 1.28 mmol) was added, and further stirred at room temperature for 1.5h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was neutralized with saturated sodium hydrogen carbonate solution, and extracted with diethyl ether. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=5/1) to give 4-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl) aniline(82%).

^1H-NMR ($CDCl_3$) δ 0.74 (3H, t, J = 7.3 Hz), 1.41 (2H, m), 1.50-3.50 (10H, br m), 1.73 (2H, m), 3.90 (2H, br), 6.60 (2H, d, J = 8.8 Hz), 7.36 (2H, d, J = 8.8 Hz)

[0066]

A mixture of 4-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)aniline (175 mg, 0.631 mmol), ethyl 4-iodobenzoate (192 mg, 0.695 mmol), cesium carbonate (288 mg, 0.884 mmol), tris(dibenzylideneacetone)dipalladium(0) (11.6 mg, 0.0127 mmol), and 2-2'-bis(diphenylphosphino)-1,1'-binaphtyl (19.6 mg, 0.0315 mmol) in dry toluene was heated at 100-110℃ for 27h. The reaction was quenched by the addition of water, the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : dichloromethane/hexane=1/1) to give light

yellow needless of ethyl 4-[4-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)-phenylaminobenzoate (53%).

^{1}H-NMR ($CDCl_3$) δ 0.77 (3H, t, J = 7.3 Hz), 1.39 (3H, t, J = 7.1 Hz), 1.44 (2H, m), 1.50-3.50 (10H, br m), 1.76 (2H, m), 4.36 (2H, q, J = 7.1 Hz), 6.15 (1H, s), 7.09 (2H, d, J = 8.8 Hz), 7.10 (2H, d, J = 8.8 Hz), 7.52 (2H, d, J = 8.8 Hz), 7.98 (2H, d, J = 8.8 Hz)

[0067]

Ethyl 4-[4-(2-Propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino]-benzoate (130 mg, 0.305 mmol) was dissolved in water (1.5 ml)-dioxane (5 ml), then concentrated sulfuric acid (1 ml) was added, and the mixture was heated at 100℃ for 15h. The mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=2/1→1/1) to give 4-[4-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino] benzoic acid (BR403)(68%).

Colorless needles (eluent : ethyl acetate/hexane)

m.p. : 216-217℃

^{1}H-NMR (DMSO-d_6) δ 0.71 (3H, t, J = 7.3 Hz), 1.36 (2H, m), 1.50-3.20 (10H, br m), 1.80 (2H, m), 7.17 (2H, d, J = 8.8 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.55 (2H, d, J = 8.8 Hz), 7.84 (2H, d, J = 8.8 Hz), 9.06 (1H, s), 12.43 (1H, s)

Anal. Calcd for $C_{18}H_{27}B_{10}NO_2$: C,54.39; H, 6.85; N, 3.52. Found C, 54.09; H, 6.64; N, 3.45.

[0068]

3-(1,2-Dicarba-*closo*-dodecaboran-1-yl)nitrobenzene was prepared from 1,2-dicarba-*closo*-dodecaborane (2.0 g, 13.9 mmol), 1.54 M n-butyl lithium/hexane solution (19.0 ml, 29.3 mmol), cuprous chloride (3.58 g, 36.2 mmol), pyridine (8.39 ml, 104 mmol), and 3-iodonitrobenzene (4.15 g, 16.7 mmol) by a similar procedure to the method applied for preparation of 4-(1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene. The residue was purified by silica gel flash column chromatography to give 3-(1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene (34%) and 3-(1,2-dicarba-*closo*-dodecaboran-1-yl)aniline (9%).

Colorless prisms

m.p. : 142-143℃

^{1}H-NMR ($CDCl_3$) δ 1.50-3.50 (10H, br m), 4.03 (1H, br s), 7.58 (1H, t, J = 8.2 Hz), 7.86 (1H, ddd, J = 1.2, 1.8, 8.2 Hz), 8.28 (1H, ddd, J = 1.2, 1.8, 8.2 Hz), 8.34 (1H, t, J = 1.8 Hz)

[0069]

3-(1,2-Dicarba-*closo*-dodecaboran-1-yl)nitrobenzene was reduced by a similar procedure that used for 4-(1,2-dicarba-*closo*-dodecaboran-1-yl)aniline. Purification by silica gel column chromatography gave 3-(1,2-dicarba-*closo*-dodecaboran-1-yl)aniline (76%).

^{1}H-NMR ($CDCl_3$) δ 1.40-3.50 (10H, br m), 3.85 (2H, br), 3.93 (1H, br s), 6.67 (1H, m), 6.78-6.81 (2H, m), 7.07 (1H, t, J = 8.2 Hz)

[0070]

3-(1,2-Dicarba-*closo*-dodecaboran-1-yl)aniline was converted to 3-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)aniline by a similar procedure that used for 4-(2-propyl-1,2-dicarba-*closo* -dodecaboran-1-yl)aniline. Purification by silica gel flash column chromatography (eluent : hexane/ethyl acetate=5/1) gave 3-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)aniline (92%).

^{1}H-NMR ($CDCl_3$) δ 0.74 (3H, t, J = 7.3 Hz), 1.43 (2H, m), 1.50-3.50 (10H, br m), 1.76 (2H, m), 3.80 (2H, br), 6.74 (1H, br d, J = 8.0 Hz), 6.91 (1H, br s), 6.98 (1H, br d, J = 8.0 Hz), 7.13 (1H, t, J = 8.0 Hz)

[0071]

Ethyl 4-[3-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino]-benzoate was prepared from 3-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)aniline by a similar procedure that used for ethyl 4-[4-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl) phenylamino]benzoate. Purification by silica gel flash column chromatography (eluent : dichloromethane/hexane = 1/1) gave light yellow crystals of ethyl 4-[3-(2-propyl-1,2-dicarba-*closo* -dodecaboran-1-yl)phenylamino]benzoate (89%).

^{1}H-NMR ($CDCl_3$) δ 0.78 (3H, t, J = 7.3 Hz), 1.39 (3H, t, J = 7.1 Hz), 1.45 (2H, m), 1.50-3.50 (10H, br m), 1.79 (2H, m), 4.36 (2H, q, J = 7.1 Hz), 6.09 (1H, s), 7.00 (2H, d, J = 8.9 Hz), 7.23 (1H, m), 7.26 (1H, m), 7.32 (1H, t, J = 7.9 Hz), 7.39 (1H, br s), 7.97 (2H, d, J = 8.9 Hz)

[0072]

This ester was hydrolyzed by a similar procedure that used for 4-[4-(2-propyl-

1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino]benzoic acid. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate = 2/1 →1/1) to give 4-[3-(2-propyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino]benzoic acid (BR453) (80%).

Colorless needles (ethyl acetate/hexane)

m.p. : 229-230℃

^{1}H-NMR (DMSO-d_6) δ 0.72 (3H, t, J = 7.3 Hz), 1.38 (2H, m), 1.50-3.20 (10H, br m), 1.84 (2H, m), 7.08 (2H, d, J = 8.8 Hz), 7.22 (1H, br d, J = 7.1 Hz), 7.34-7.41 (3H, m), 7.83 (2H, d, J = 8.8 Hz), 8.94 (1H, s), 12.38 (1H, s)

[0073]

Example 6

4-(2-Methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)nitrobenzene (349 mg, 1.25 mmol) was dissolved in ethanol (25 ml) and hydrogenated at room temperature for 1h under the atmospheric pressure of hydrogen using 10% Pd/C (87 mg),. After the catalyst was removed by filtration, the filtrate was concentrated to give 4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl) aniline (95%).

^{1}H-NMR ($CDCl_3$) δ :1.40-3.50 (10H, br m), 1.68 (3H, s), 4.01 (2H, br), 6.62 (2H, d, J = 8.6 Hz), 7.39 (2H, d, J = 8.6 Hz).

A mixture of 4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)aniline (174 mg, 0.698 mmol), 4-iodo ethyl benzoate (193 mg, 0.699 mmol), cesium carbonate (318 mg, 0.976 mmol), tris (dibenzylidene acetone) dipalladium (0)(12.8 mg, 0.0140 mmol), and 2-2'-bis(diphenylphosphino)-1,1'-binaphtyl (21.7 mg, 0.0348 mmol) in dry toluene was heated at 110℃ for 24h. The reaction was quenched by the addition of water, and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : dichloromethane /hexane =1/1) to give light yellow needles of ethyl 4-[4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenyl-amino] benzoate (71%).

^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, br m), 1.39 (3H, t, J = 7.1 Hz), 1.72 (3H, s), 4.36 (2H, q, J = 7.1 Hz), 6.15 (1H, br s), 7.09 (4H, d, J = 8.8 Hz), 7.54 (2H, d, J = 8.8 Hz), 7.98 (2H, d, J = 8.8 Hz).

[0074]

Ethyl 4-[4-(2-Methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino]-benzoate (95 mg, 0.239 mmol) was dissolved in THF(3 ml), 1N potassium hydroxide (1.20 ml) was added, and refluxed for 27h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=2/1) to give 4-[4-(2-methyl-1,2-dicarba-*closo*-dodeca-boran-1-yl) phenylamino] benzoic acid (BR401)(31%), and ethyl 4-[4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino]benzoate was recovered (27%).

BR401 : Colorless needles (ethyl acetate/hexane)

m.p. : 258-260℃

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 1.73 (3H, s), 7.16 (2H, d, J = 8.8 Hz), 7.20 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.83 (2H, d, J = 8.8 Hz), 9.06 (1H, s), 12.42 (1H, br)

Anal. Calcd for $C_{16}H_{23}B_{10}NO_3$: C, 52.01; H, 6.27; N, 3.79. Found C, 52.11; H, 6.54; N, 3.64.

[0075]

BR431 was synthesized from [4-(1,2-dicarba-*closo*-dodecaboran -1-yl)-2-methyl nitrobenzene by a similar procedure that used for ethyl 4-[4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)phenylamino]benzoate. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=5/1→3/1) to give light orange needless of ethyl 4-{4-(1,2-dicarba-*closo*-dodecaboran-1-yl)-2-methy}-phenylamino]benzoate (61%).

^{1}H-NMR ($CDCl_3$) δ :1.38 (3H, t, J = 7.2 Hz), 1.50-3.50 (10H, br m), 2.26 (3H, s), 3.92 (1H, br s), 4.35 (2H, q, J = 7.2 Hz), 5.70 (1H, s), 6.95 (2H, d, J = 9.0 Hz), 7.23 (1H, d, J = 8.8 Hz), 7.27 (2H, dd, J = 2.4, 8.8 Hz), 7.33 (1H, d, J = 2.4 Hz), 7.95 (2H, d, J = 9.0 Hz).

[0076]

Sodium hydride (33.2 mg, 0.830 mmol) was suspended in DMF (1 ml), and ethyl 4-{4-(1,2-dicarba-*closo*-dodecaboran-1-yl)-2-methy}phenylamino] benzoate (150 mg, 0.377 mmol) in DMF (3 ml) was added to the suspension. The mixture was stirred at room temperature for 5 min, methyl iodide (161 mg, 1.13 mmol) was added, and

further stirred at room temperature for 20 min. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with diethyl ether. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=10/1) to give ethyl 4-{N-methyl-[2-methyl-4-(2 -methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)]phenylamino}benzoate (74%).
^{1}H-NMR ($CDCl_3$) δ :1.35 (3H, t, J = 7.1 Hz), 1.50-3.50 (10H, br m), 1.76 (3H, s), 2.14 (3H, s), 3.28 (3H, s), 4.35 (2H, q, J = 7.1 Hz), 6.48 (2H, d, J = 9.2 Hz), 7.16 (1H, d, J = 8.4 Hz), 7.53 (1H, dd, J = 2.4, 8.4 Hz), 7.57 (1H, d, J = 2.4 Hz), 7.88 (2H, d, J = 9.2 Hz).

[0077]

Ethyl 4-[N-Methyl-[2-methyl-4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)]phenylamino] ethyl benzoate (111 mg, 0.261 mmol) was dissolved in THF (3 ml), 1N potassium hydroxide (1.95 ml) was added, and refluxed for 26h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=2/1) to give 4-{N-methyl-[2-methyl-4-(2-methyl-1,2 -dicarba-*closo*-dodecaboran-1-yl)] phenylamino} benzoic acid (BR431) (12%), and ethyl 4-[N-methyl-[2 -methyl-4-(2-methyl-1,2-dicarba-*closo*-dodecaboran-1-yl)] phenylamino]benzoate was recovered (16%).

BR431 : Colorless needles (ethyl acetate/hexane)

m.p. : 296-298℃

^{1}H-NMR (DMSO-d_6) δ :1.40-3.20 (10H, br m), 1.80 (3H, s), 1.99 (3H, s), 3.24 (3H, s), 6.51 (2H, d, J = 9.1 Hz), 7.31 (1H, d, J = 8.3 Hz), 7.63 (1H, dd, J = 2.5, 8.3 Hz), 7.69 (1H, d, J = 2.5 Hz), 7.74 (2H, d, J = 9.1 Hz), 12.18 (1H, br s)

Anal. Calcd for $C_{16}H_{23}B_{10}NO_3$: C, 54.39; H, 6.85; N, 3.52. Found C, 54.25; H, 6.95; N, 3.53.

[0078]

Example 7

1,12-Dicarba-*closo*-dodecaborane (3.5 g, 24.3 mmol) was dissolved in DME, 1.54 M n-butyl lithium/hexane solution (16.6 ml, 25.6 mmol) was added dropwise at 0℃ under argon atmosphere. The mixture was stirred at room temperature for 30

min, cuprous chloride (3.13 g, 31.6 mmol) was added in one portion, and further stirred at room temperature for 1h. Then, pyridine (14.7 ml, 183 mmol) was added, and 4-iodo anisole (5.97 g, 25.5 mmol) was added in one portion, and heated at 100℃ for 48h. After cooling, the mixture was diluted with diethyl ether, then stirred at room temperature for 3h, and insoluble substance was separated by filtration with Celite. The filtrate was washed with 2N hydrochloric acid, $Na_2S_2O_3$ solution, water, and brine in order, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane→hexane/ethyl acetate=10/1) to give 1-(4-methoxyphenyl)-1,12-dicarba-*closo*-dodecaborane(O-methy-BE100)(60%) and 1,12-bis (4-methoxy phenyl)-1,12-dicarba-*closo*-dodecaborane (O,O'-dimethyl-BE160)(13%).

O-methy-BE100 : Colorless needles ; ^{1}H-NMR ($CDCl_3$) δ :1.50-3.30 (10H, br m), 2.75 (1H, br s), 3.74 (3H, s), 6.68 (2H, d, J = 9.1 Hz), 7.11 (2H, d, J = 9.1 Hz).

O, O'-dimethyl-B E 160 : Colorless needles ; ^{1}H-NMR ($CDCl_3$) δ :1.50-3.50 (10H, br m), 3.75 (6H, s), 6.69 (4H, d, J = 9.0 Hz), 7.15 (4H, d, J = 9.0 Hz).

[0079]

O-Methyl-BE100 (100 mg, 0.399 mmol) was dissolved in dichloromethane (1 ml), 1M boron tribromide/dichloro methane solution (0.48 ml) was added dropwise under cooling with dry ice/acetone, and stirred at room temperature for 2h. The mixture was poured into ice water, and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=10/1) to give 1-(4 -hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (BE100) (93%).

Colorless needles (dichloromethane/hexane)

m.p. : 193-194℃

^{1}H-NMR ($CDCl_3$) δ :1.40-3.20 (10 H, br m), 2.75 (1H, br s), 4.73 (1H, br s), 6.61 (2H, d, J = 9.0 Hz), 7.07 (2H, d, J = 9.0 Hz)

HRMS Calcd for $C_8H_{16}B_{10}O$ 236.2204, Found 236.2227

[0080]

O,O'-Dimethyl-BE160 (150 mg, 0.421 mmol) was dissolved in dichloro-methane(5 ml), 1M boron tribromide/dichloromethane solution (1.05 ml) was added

dropwise under cooling with dry ice/acetone, and stirred at room temperature for 2h. The mixture was poured into ice water, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=5/1) to give 1,12-bis(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (BE160) (93%).

Colorless prisms (ethyl acetate/hexane)

m.p.: 292-294℃ ; ^{1}H-NMR (DMSO-d_6) δ : 1.70-3.30 (10H, br m), 6.60 (4H, d, J = 8.9 Hz), 7.00 (4H, d, J = 8.9 Hz) 9.63 (2H, s)

HRMS Calcd for $C_{14}H_{20}B_{10}O_2$ 328.2466, Found 328.2480

[0081]

Example 8

O-Methyl-BE100 (500 mg, 2.00mmol) was dissolved in benzene/diethyl ether (2:1, 15 ml), 1.54M n-butyl lithium/hexane solution (1.56 ml, 2.40 mmol) was added dropwise at 0℃ under argon atmosphere, then stirred at room temperature for 30 min. The mixture was cooled to 0℃, methyl chloroformate (227 mg, 2.40 mmol) was added dropwise, and stirred at room temperature for 3h. The reaction was quenched by the addition of water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=50/1) to give 1-methoxycarbonyl-12-(4- methoxyphenyl-1,12-dicarba-*closo*-dodecaborane (O-methyl-BE110) (91%).

Colorless needles

^{1}H-NMR (CDCl$_3$) δ :1.60-3.40 (10 H, br m), 3.65 (3H, s), 3.74 (3H, s), 6.68 (2H, d, J = 9.1 Hz), 7.08 (2H, d, J = 9.1 Hz).

[0082]

O-Methyl-BE110 was demethylated by a similar procedure that used for BE160. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=6/1) to give 1-methoxycarbonyl-12-(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (BE110)(99%).

Colorless prisms (dichloromethane/hexane)

m.p. : 178-179℃

^{1}H-NMR ($CDCl_3$) δ :1.60-3.40 (10H, br m), 3.65 (3H, s), 4.84 (1H, br), 6.61 (2H, d, J = 9.0 Hz), 7.04 (2H, d, J = 9.0 Hz)

HRMS Calcd for $C_{10}H_{18}B_{10}O_3$ 294.2259, Found 294.2265

[0083]

To a suspension of lithium aluminum hydride (25.8 mg, 0.680 mmol) in THF (3 ml), O-methyl-BE110 (150 mg, 0.486 mmol) in THF (2 ml) was added dropwise at 0℃, then stirred at room temperature for 2.5 h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated to give 1-hydroxymethyl-12-(4-methoxyphenyl)-1,12-dicarba-*closo*-dodecaborane (O-methyl-BE120) (99%).

Colorless needles ; ^{1}H-NMR ($CDCl_3$) δ : 1.50-3.30 (10H, br m), 3.54 (2H, s), 3.74 (3H, s), 6.68 (2H, d, J = 9.2 Hz), 7.11 (2H, d, J = 9.2 Hz).

O-Methyl-BE120 was demethylated by a similar procedure that used for BE160. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=4/1) to give 1-hydroxymethyl-12-(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (BE120) (100%).

Colorless needles (dichloromethane/hexane) ; m.p. : 184-185℃ ; ^{1}H-NMR ($CDCl_3$) δ : 1.50-3.30 (10H, br m), 3.54 (2H, s), 4.87 (1H, br), 6.61 (2H, d, J = 8.9 Hz), 7.06 (2H, d, J = 8.9 Hz) ; HRMS Calcd for $C_9H_{18}B_{10}O_2$ 266.2310, Found 266.2310

[0084]

Example 9

O-Methyl-BE110 (260 mg, 0.843 mmol) was dissolved in THF (3ml), 1N potassium hydroxide (4.22 ml) was added, and stirred at room temperature for 17h. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and then brine, dried over sodium sulfate and concentrated to give 1-hydroxycarbonyl-12-(4-methoxyphenyl)-1,12-dicarba-*closo*-dodecaborane (O-methyl-BE130) (quantitatively).

Colorless needles ; ^{1}H-NMR (DMSO-d_6) δ :1.60-3.40 (10H, br m), 3.69 (3H, s), 6.78 (2H, d, J = 9.1 Hz), 7.08 (2H, d, J = 9.1 Hz), 14.06 (1H, br).

O-Methyl-BE130 was demethylated by a similar procedure that used for BE160 to give 1-hydroxycarbonyl-12-(4-hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (BE130).

Colorless needles (ethyl acetate/dichloromethane/hexane) ; m.p. : >300℃ ; ^{1}H-NMR (DMSO-d_6) δ :1.60-3.40 (10H, br m), 6.57 (2H, d, J = 8.8 Hz), 6.94 (2H, d, J = 8.8 Hz), 9.58 (1H, s).

[0085]

A mixture of BE130 (50 mg, 0.170 mmol), triethylamine (51.6 mg, 0.510 mmol), DMAP (2.1 mg, 0.0172 mmol), and DPPA (70.1 mg, 0.254 mmol) in t-butanol (3 ml) was refluxed for 24h. The mixture was concentrated, and the residue was dissolved in ethyl acetate. The product was washed with water then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=20/1) to give 1-tert-butoxycarbonyl-amino-12-(4-methoxyphenyl)-1,12 -dicarba-*closo*-dodecaborane (41%).

Colorless needles ; ^{1}H-NMR ($CDCl_3$) δ :1.39 (9H, s), 1.60-3.40 (10H, br m), 3.73 (3H, s), 4.89 (1H,s), 6.67 (2H, d, J = 9.0 Hz), 7.11 (2H, d, J = 9.0 Hz).

The Boc protected product obtained above (62 mg, 0.170 mmol) was dissolved in dichloromethane (2 ml), TFA (0.4 ml) was added, and stirred at room temperature for 2.5h. The reaction was quenched by the addition of saturated sodium hydrogen carbonate solution, and the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give 1-amino-12-(4-methoxyphenyl)-1,12-dicarba-*closo*-dodecaborane (O-methyl-BE140) (100%).

Colorless needles

^{1}H-NMR ($CDCl_3$) δ :1.50-3.30 (10H, br m), 3.73 (3H, s), 6.67 (2H, d, J = 9.0 Hz), 7.11 (2H, d, J = 9.0 Hz).

[0086]

O-Methyl-BE140 was demethylated by a similar procedure that used for BE160. The mixture was poured into cool saturated sodium hydrogencarbonate solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel

flash column chromatography (eluent : hexane/ethyl acetate=5/1) to give 1-amino-12-(4-hydroxyphenyl)-1,12 -dicarba-*closo*-dodecaborane (BE140) (100%).

Colorless needles (dichloromethane/hexane)

m.p. : 169-171℃

^{1}H-NMR ($CDCl_3$) δ : 1.50-3.30 (10H, br m), 2.05 (2H, br s), 4.81 (1H, s), 6.59 (2H, d, J = 9.0 Hz), 7.06 (2H, d, J = 9.0 Hz)

HRMS Calcd for $C_8H_{17}B_{10}NO$ 251.2313, Found 251.2299

[0087]

Example 10

O-Methyl-BE100 (500 mg, 2.00 mmol) was dissolved in diethyl ether (5 ml), 1.54M n-butyl lithium/hexane solution (1.56 ml, 2.40 mmol) was added dropwise at 0℃ under argon atmosphere, and then stirred at room temperature for 2h. Acetyl chloride (236 mg, 3.01 mmol) was dissolved in THF (1 ml) and added dropwise under cooling with dry ice/acetone bath, then stirred at room temperature for 18h. The reaction was quenched by the addition of water, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane→hexane/ethyl acetate=30/1) to give 1-acetyl-12-(4-methoxy)-1,12-dicarba-*closo*-dodecaborane (O-methyl-BE150) (12%) and the starting material (67%).

Colorless needles

^{1}H-NMR ($CDCl_3$) δ :1.60-3.40 (10H, br m), 2.11 (3H, s), 3.74 (3H, s), 6.68 (2H, d, J = 9.1 Hz), 7.09 (2H, d, J = 9.1 Hz).

[0088]

O-Methyl-BE150 was demethylated by a similar procedure that used for BE160. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=5/1) to give 1-acetyl-12-(4-hydroxyphenyl) -1,12-dicarba-*closo*-dodecaborane (BE150) (19%).

Colorless needles (dichloromethane/hexane)

^{1}H-NMR ($CDCl_3$) δ :1.50-3.30 (10H, br m), 2.11 (3H, s), 4.85 (1H, s), 6.62 (2H, d, J = 8.9 Hz), 7.05 (2H, d, J = 8.9 Hz).

[0089]

O-Methyl-BE150 (70 mg, 0.239 mmol) was suspended in ethanol (3 ml), sodium boron hydride (4.52 mg, 0.119 mmol) was added, and stirred at room temperature for 30 min. The reaction was quenched by the addition of 2N hydrochloric acid, and the mixture was extracted with ethyl acetate. The organic layer was washed with water then brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=10/1) to give 1-hydroxyethyl-12-(4-methoxyphenyl)-1,12-dicarba-*closo*-dodecaborane (O-methyl-BE121) (78%).

Colorless needles

^{1}H-NMR ($CDCl_3$) δ : 1.11 (3H, d, J = 6.4 Hz), 1.50-3.30 (10H, br m), 3.74 (1H, q, J = 6.4 Hz), 3.74 (3H, s), 6.68 (2H, d, J = 9.1 Hz), 7.11 (2H, d, J = 9.1 Hz).

[0090]

O-Methyl-BE121 was demethylated by a similar procedure that used for BE160. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=5/1) to give 1-hydroxyethyl-12-(4 -hydroxyphenyl)-1,12-dicarba-*closo*-dodecaborane (BE121) (94%).

Colorless flakes (dichloromethane/hexane)

m.p. : 173-174℃

^{1}H-NMR ($CDCl_3$) δ :1.11 (3H, d, J = 6.4 Hz), 1.50-3.30 (10H, br m), 3.74 (1H, q, J = 6.4 Hz), 4.84 (1H, br), 6.61 (2H, d, J = 9.0 Hz), 7.07 (2H, d, J = 9.1 Hz)

HRMS Calcd for $C_{10}H_{20}B_{10}O_2$ 280.2466, Found 280.2466

[0091]

Example 11

1,12-Dicarba-*closo*-dodecaborane (3.5 g, 24.3 mmol) was dissolved in DME, 1.54 M n-butyl lithium/hexane solution (16.6 ml, 25.6 mmol) was added dropwise at 0℃ under argon atmosphere. The mixture was stirred at room temperature for 30 min, cuprous chloride (3.13 g, 31.6 mmol) was added in one portion, and further stirred at room temperature for 1h. Then, pyridine (14.7 ml, 183 mmol) was added, 4-iodoanisole (5.97 g, 25.5 mmol) was added in one portion, and heated at 100℃ for 48h. After cooling, the mixture was diluted with diethyl ether, stirred at room temperature for 3h, and insoluble substance was separated by filtration with Celite. The filtrate was washed with 2N hydrochloric acid, $Na_2S_2O_3$ solution, water, and brine

in order, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (eluent : hexane→hexane/ethyl acetate=30/1) to give 1-(4-methoxyphenyl)-1,7-dicarba-*closo*-dodecaborane (O-methyl-BE200) (41%) and 1,7-bis(4-methoxyphenyl)-1,7-dicarba-*closo*-dodecaborane (O, O'-dimethyl-BE260) (17%).

O-methyl-BE200

Colorless needles

^{1}H-NMR ($CDCl_3$) δ :1.50-3.70 (10H, br m), 3.04 (1H, br s), 3.77 (3H, s), 6.76 (2H, d, J = 9.2 Hz), 7.33 (2H, d, J = 9.2 Hz).

O,O'-dimethyl-BE260

Colorless needles

^{1}H-NMR ($CDCl_3$) δ :1.50-3.70 (10H, br m), 3.78 (6H, s), 6.77 (4H, d, J = 9.0 Hz), 7.37 (4H, d, J = 9.0 Hz).

[0092]

O-Methyl-BE200 was demethylated by a similar procedure that used for BE100. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=10/1) to give 1-(4-hydroxyphenyl)-1,7-dicarba-*closo*-dodecaborane (BE200) (92%).

Colorless needles (dichloromethane/hexane)

m.p. : 180-181℃

^{1}H-NMR ($CDCl_3$) δ :1.50-3.70 (10H, br m), 3.04 (1H, br s), 4.81 (1H, s), 6.69 (2H, d, J = 8.9 Hz), 7.28 (2H, d, J = 8.9 Hz).

[0093]

O, O'-Dimethyl-BE260 was demethylated by a similar procedure that used for BE160. The product was purified by silica gel flash column chromatography (eluent : hexane/ethyl acetate=3/1) to give 1,7-bis(4-hydroxyphenyl)-1,7-dicarba-*closo*-dodecaborane (BE260) (85%).

Colorless needles (ethyl acetate/hexane)

m.p. : 198-199℃

^{1}H-NMR (DMSO-d_6) δ :1.50-3.80 (10H, br m), 6.68 (4H, d, J = 8.9 Hz), 7.26 (4H, d, J = 8.9 Hz), 9.73 (2H, s)

Anal. Calcd for $C_{14}H_{20}B_{10}O_2$: C, 51.20; H, 6.14. Found C, 51.14; H, 6.07.

[0094]

Test Example

Anti-leukemia activity test and estrogen activity test were performed on nuclear receptor regulators having a dicarba-*closo*-dodecaborane structure of the present invention obtained in the examples.

(1) Anti-leukemia Activity

Inhibitory activity against proliferation of human promyelocytic leukemia cell strain HL-60 was evaluated an index of anti-leukemia activity. Subcultured HL-60 cells were seeded with the initial cell number of 8×10^4 cells/ml in the RPMI 1640 medium containing bovine fetal serum and an antibiotics. Each test compound was added at various concentrations and the mixture was cultured at 37℃. Four days later, cell number was counted. Anti-leukemia activity of each test compound was shown in the tables as percentage values of differentiated cells, which cells were not differentiated in the absence of the test drug, in the presence of 1 mM of the test compound based on morphological change observation and NBT reducing ability of the cells as indexes. Table 1 shows the results obtained by experiments wherein only the test compounds were added. BR401, BR403, and BR453 were found to have strong differentiation inducing activities and the activities were maintained at 0.01 μM concentration of the test compounds. Table 2 shows the results of experiments with coexistence of the compound AM80 as a differentiation inducing agent (4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carbamoyl]benzoic acid). As a result, BR201 was found to have a strong anti-differentiation activity. Table 3 shows the results of experiments with coexistence of the compound HX630 (4-[2,3-(2,5-dimethyl-2,5-hexano)dibenzo-[b,f]-[1,4]thiazepin-11-yl]benzoic acid) which is inactive per se but enhances the action of differentiation inducing substances. As a result, BR110, BR251, and BR350 were found to have differentiation inducing activities.

[0095]

[Table 1]

Test Compound 1 μ M	No coexisting compound (control:<10)
BR10	8
BR20	12
BR30	7
BR110	12
BR201	11
BR251	8
BR300	6
BR350	11
BR401	70
BR403	82
BR431	10
BR453	80
BR401*	26
BR403*	84
BR453*	80

*Test Compound 0.01 μ M

[0096]

[Table 2]

Test Compound	Coexisting compound Am80 3.3×10^{-10}M (control: 55)
BR10	65
BR20	70
BR30	66
BR110	60
BR201	5
BR251	55
BR300	37
BR350	60
BR401	60
BR431	55

[0097]

[Table 3]

Test Compound	Coexisting Compound HX630 1×10^{-7}M (control: <10)
BR10	7
BR20	10
BR30	9
BR110	48
BR201	12
BR251	77
BR300	8
BR350	48
BR401	75
BR431	12

[0098]

(2) Estrogenic Activity

As estrogenic activity, estrogen receptor-dependent transcriptional activation abilities of the test compounds were determined by the reporter gene assay using luciferase gene. COS-1 cells were cultured using a DMEM medium containing an antibiotics and 5% bovine fetal serum in the wells of 24 well plates (cell density : 5 to 6 $\times 10^4$/well) at 37℃ for one night under 5% carbon dioxide. On the next day, the medium was changed to DMEM medium not containing Phenol Red. Using gene introducing reagent Tfx-20 (Promega), reporter plasmid EREx3-pGL-TK, in which rat estrogen receptor expression plasmid pCI-rERα and an estrogen responsive sequence were placed upstream of the luciferase gene, and β-galactosidase expression plasmid pCMVβ used as an internal standard were introduced into cells. The cells were cultured for 2h, and the medium was changed to DMEM not containing Phenol Red but containing active charcoal-treated serum.

[0099]

The culture was added with each test compound dissolved in ethanol at various concentrations (final ethanol concentration at 0.5%) and then cultivation was continued at 37℃ for one night under 5% carbon dioxide. On the next day, the cells were lysed and enzymatic activity of luciferase expressed was measured by using a chemiluminometer. The values were standardized based on galactocidase enzymatic activity, and then compared with the values obtained by experiments using no test

compound and used as values of activity at various concentrations. Table 4 shows estrogenic activities. The estrogenic activities in the table are shown as concentrations for 50% activity (EC_{50} values) which give 50% activities relative to luciferase activity regarded as 100 that is expressed by treatment with the control compound β-estradiol at 10 nM. Each compound tested in this experiment has a high estrogenic activity. In particular, BE100, BE120, BE121, and BE140 have much higher activity than that of β-estradiol used as the control.

[0100]

[Table 4]

Test Compound	EC_{50} Value (nM)
BE100	0.7
BE110	2.0
BE120	0.05
BE121	1.0
BE130	10
BE140	0.5
BE160	1.0
BE200	2.0
BE260	1.0

[0101]

[Effect of the Invention]

The compounds represented by the aforementioned formula (I) or physiologically acceptable salts thereof have physiological activities such as retinoid activities, and therefore, medicaments of the present invention comprising said substance as an active ingredients are useful for the treatment of leukemia and the like.